pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

The CADTH pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug reimbursement decisions. The pCODR process brings consistency and clarity to the assessment of cancer drugs by looking at clinical evidence, cost-effectiveness, and patient perspectives.

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

Drug: Isatuximab (Sarclisa)

Submitted Reimbursement Request: Isatuximab in combination with pomalidomide and dexamethasone, for the treatment of patients with relapsed or refractory multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor.

Submitted By:	**Manufactured By:**
Sanofi Genzyme	Sanofi Genzyme
NOC Date:	**Submission Date:**
April 29, 2020	August 17, 2020
Initial Recommendation:	**Final Recommendation:**
February 4, 2021	April 1, 2021

Approximate per patient drug costs, per month (28 days)	Dosing and administration per 28-day cycle: • Isatuximab 6 mL (100 mg/5 mL) and 30 mL (500 mg/25 mL) intravenous injections cost $757.90 and $3,789.49, respectively • Pomalidomide 4 mg capsule costs $500.00 • Dexamethasone 4 mg tablet costs $0.3046 • Isatuximab 10 mg/kg administered 4 times in cycle 1 costs $21,221 • Isatuximab 10 mg/kg administered twice per cycle for subsequent cycles costs $10, 611 per cycle • Pomalidomide costs $10,500 per cycle Isatuximab administered with pomalidomide and dexamethasone costs $31,727 to $31,733 for cycle 1, and $21,117 to $21,123 per cycle for subsequent cycles.

pERC RECOMMENDATION

☐ **Reimburse**

☒ **Reimburse with clinical criteria and/or conditions[a]**

☐ **Do not reimburse**

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

pERC conditionally recommends the reimbursement of isatuximab (Sarclisa) in combination with pomalidomide and dexamethasone (IsaPd) in patients with relapsed or refractory multiple myeloma (RRMM) who have received at least 2 prior lines of therapy including lenalidomide and a proteasome inhibitor (PI), if the following conditions are met:

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

Eligible patients include adults with RRMM who have failed treatment on lenalidomide and a proteosome inhibitor, administered either alone or in combination in any prior line of treatment, have disease that was refractory to the last line of treatment received, and good performance status. Treatment should be continued until unacceptable toxicity or disease progression.

pERC made this recommendation because it was satisfied that there is a net overall clinical benefit with IsaPd compared to pomalidomide and

	dexamethasone (Pd) alone based on statistically significant and clinically meaningful improvements in progression-free survival (PFS) and overall response rate (ORR), manageable toxicities, and maintenance of quality of life (QoL) based on descriptive analyses. pERC also concluded that IsaPd aligns with the following patient values: delays disease progression, maintains QoL, has manageable side effects, and offers an additional effective treatment option. pERC concluded that, at the submitted price, IsaPd is not cost-effective when compared to Pd. The results of the cost-effectiveness analysis were driven by the high cost of isatuximab and pomalidomide. Even with a price reduction for both isatuximab and pomalidomide, it is highly unlikely that IsaPd would be cost-effective at a willingness-to-pay threshold of $50,000 per quality-adjusted life-year (QALY) gained. The cost-effectiveness of IsaPd compared to other relevant (and lower cost) comparator regimens, such as carfilzomib and dexamethasone (Kd) and Pd plus cyclophosphamide, remains unknown at this time given the lack of evidence on its comparative effectiveness.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Pricing Arrangements to Improve Cost-Effectiveness and Affordability of IsaPd** Given that pERC was satisfied that there is a net clinical benefit of IsaPd compared with Pd, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness and affordability of IsaPd compared with other treatment options for RRMM. pERC concluded that a reduction in the drug price of both isatuximab and pomalidomide would be required to improve the cost-effectiveness of IsaPd to an acceptable level and to decrease the budget impact. **Optimal Sequencing of IsaPd with Other Therapies for RRMM including Daratumumab** pERC noted that the eligibility criteria in the ICARIA-MM trial included patients who had previous treatment with but were not refractory to an anti-CD38 monoclonal antibody (mAb), but that only 1 patient in the IsaPd treatment group of the trial had prior exposure to an anti-CD38 mAb (i.e., daratumumab). In the absence of evidence, pERC concluded that the efficacy of IsaPd in eligible patients who have received at least 2 prior lines of therapy that includes daratumumab is unknown. pERC also concluded that due to the absence of evidence on sequencing of IsaPd and currently available treatments for RRMM, no informed recommendation on optimal sequencing could be made. pERC recognized that jurisdictions would need to address this issue upon implementation of IsaPd reimbursement and noted that collaboration among jurisdictions to develop a common approach to sequencing would be of value. **Please note:** Provincial Advisory Group (PAG) questions are addressed in detail in the Summary of pERC Deliberations and in a summary table in Appendix 1.

SUMMARY OF pERC DELIBERATIONS

pERC's *Deliberative Framework* for drug reimbursement recommendations focuses on four main criteria:	
CLINICAL BENEFIT	**PATIENT-BASED VALUES**
ECONOMIC EVALUATION	**ADOPTION FEASIBILITY**

Despite significant advancements in the treatment and life expectancy of patients with multiple myeloma (MM), it remains an incurable disease. Regardless of the choice and duration of initial therapy, most patients eventually relapse, and further therapy is required. As MM advances, patients become increasingly refractory to treatment as the ability to achieve a response declines, and the durability of response and length of treatment-free intervals shorten with successive lines of therapy.

Current standard treatment options for patients with relapsed or refractory MM (RRMM) include daratumumab and dexamethasone with either bortezomib (DVd) or lenalidomide (DRd), Pd with or without cyclophosphamide, and carfilzomib in combination with dexamethasone (Kd). There is no strong evidence from randomized control trials (RCTs) supporting the preferential use of one of these treatments over another. Clinically, the adopted treatment sequence is largely driven by patient factors (i.e., prior therapy received and response) and provincial funding. In most jurisdictions, the predominant second-line therapy in patients with RRMM is DVd or DRd; however, funding of daratumumab is dependent on sensitivity to either bortezomib or lenalidomide where it must be used in the triple combination. pERC acknowledged that isatuximab would fulfill an unmet need among patients who are monoclonal antibody (mAb) naive but ineligible to receive daratumumab. While efficacious therapeutic options exist for patients with RRMM, pERC agreed with the Clinical Guidance Panel (CGP) and patients providing input for this submission, that given the incurable nature of MM, there is a need to identify additional therapies that are active in subsequent lines of treatment.

pERC deliberated on the results of 1 ongoing, international, open-label, phase III RCT, ICARIA-MM, that compared isatuximab in combination with pomalidomide and dexamethasone (IsaPd) to Pd alone in patients with RRMM who had received at least 2 prior lines of therapy that included lenalidomide and a proteasome inhibitor (PI). pERC noted that enrolled patients had MM that progressed after treatment with lenalidomide and a PI, whether these agents were given alone or in combination; and patients had to be refractory to their last received line of treatment but must have achieved a minimal response or better to at least 1 prior line of therapy. pERC also noted that patients who had prior treatment with an anti-CD38 mAb were eligible for the trial provided their disease was not refractory to the treatment. pERC discussed that patients in the ICARIA-MM trial represented a heavily pre-treated patient population where the median number of previous lines of treatment was 3 (range 2 to 11) and a sizable proportion of patients (34.9%) had received 4 or more prior lines of therapy; however, only 1 trial patient had prior exposure to an anti-CD38 mAb and therefore the efficacy of IsaPd in patients pre-treated with an anti-CD38 mAb remains uncertain. pERC discussed that the trial demonstrated superior treatment efficacy with IsaPd when compared to Pd alone based on blinded independent central review (IRC) outcome assessment, and pERC considered the statistically significant improvements in PFS and ORR observed with IsaPd to be clinically meaningful. However, pERC acknowledged that the trial follow-up period was short (11.6 months) and data on overall survival (OS) are currently immature. At the time of the interim analysis, the median OS had not been reached in either treatment group. Consequently, the magnitude of a potential OS benefit with IsaPd is uncertain and will require confirmation based on longer follow-up data. pERC noted that although treatment crossover was not permitted in the trial, long-term OS will be confounded by the use of subsequent anti-cancer therapies in both treatment groups that included a higher proportion of patients treated with daratumumab in the Pd group. However, pERC agreed with CGP that PFS is a relevant and validated outcome in RRMM that has been used to support previous reimbursement submissions in MM. In addition, pERC noted that subgroup analyses of the primary outcome of PFS, as well as other efficacy outcomes assessed (time-to-progression, duration of response) were all consistent and favoured treatment with IsaPd.

pERC discussed the available data on patient-reported outcomes (PRO) from the ICARIA-MM trial, which were pre-specified secondary outcomes that were analyzed descriptively. pERC noted that the trial assessed various measures of QoL using multiple PRO questionnaires that included global health

status/QoL, patient functioning, and disease and treatment-related symptoms. The PRO data from each questionnaire showed that while on treatment there were no clinically important mean changes in score from baseline in either treatment group that met pre-specified thresholds of clinically meaningful change. pERC considered the input received from patients that identified improved QoL as an outcome highly valued by patients when contemplating new myeloma treatment. Based on the QoL data that showed no detriment in health-related QoL and related symptoms with either IsaPd or Pd, pERC concluded that QoL was maintained among patients treated with IsaPd in the trial.

pERC also deliberated on the safety profile of IsaPd compared to Pd. pERC noted that the median duration of treatment exposure was longer in the IsaPd treatment group (41 weeks) compared to the Pd group (21 weeks) and there was a greater frequency of dose reductions of both pomalidomide and dexamethasone, as well as treatment cycle delays in patients treated with IsaPd. pERC discussed the higher incidence of grade ≥ 3 and serious adverse events (AEs), both unrelated and related to study treatment, in patients treated with IsaPd but noted that the proportions of patients who discontinued study treatment or who died due to a drug-related AE were small in the trial and similar in each treatment group. When compared to Pd, infusion-related reactions, neutropenia, upper respiratory infections, bronchitis, and febrile neutropenia were the most common AEs that occurred with greater frequency in patients treated with IsaPd. pERC noted that most infusion-related reactions in the trial occurred at the start of treatment and were reversible using protocol defined premedications. Based on these safety data, pERC agreed with the CGP and registered clinicians providing input for this submission that despite the overall greater toxicity associated with the triplet combination, the safety profile of IsaPd appears manageable and generally well tolerated by patients.

Considering the evidence from the ICARIA-MM trial, pERC concluded that there is a net overall clinical benefit of IsaPd when compared to Pd alone based on clinically meaningful improvements in PFS and ORR, maintenance of QoL, and manageable toxicities.

In addition to the ICARIA-MM trial, pERC also deliberated on the results of an indirect treatment comparison (ITC) submitted by the sponsor to estimate the comparative efficacy of IsaPd to Kd, which was identified as a relevant comparator by the CGP, registered clinicians, and the Provincial Advisory Group (PAG). In the absence of direct evidence comparing these treatments, the ITC was included in the submission to CADTH to inform the pharmacoeconomic model supporting the reimbursement request. pERC noted that the ITC performed was limited to efficacy outcomes (PFS and OS) based on the results of the ICARIA-MM trial and the ENDEAVOR trial, which compared Kd to bortezomib and dexamethasone. The sponsor acknowledged that the available data prevented the use of a more robust method of analysis. Different inclusion criteria between the 2 trials resulted in differences in important treatment effect modifiers (e.g., number and types of prior lines of therapy received) that were not accounted for in the unadjusted and unanchored ITC that was performed. pERC agreed with the CADTH Methods Team that this limitation of the ITC has the potential to severely bias the results obtained, and as such, no conclusions can be drawn regarding the comparative efficacy of IsaPd and Kd based on the submitted ITC.

pERC deliberated on the patient advocacy input that was received from 1 patient group concerning IsaPd. pERC discussed that from the patient's perspective, RRMM has a significant impact on QoL resulting from physical symptoms of the disease and from treatments (specifically mobility, neuropathy, shortness of breath, and fatigue) that affect social well-being, participation in activities, and have financial implications that include loss of income due to absences from work and out of pocket expenses related to treatment. pERC noted that patients value treatments for MM that effectively control their disease with fewer side effects and improve their QoL. Considering the natural history of MM, which is characterized by remissions followed inevitably by relapse, patients emphasized that they also value treatment choice and desire access to a variety of effective treatments that improve prognosis. The patient advocacy input included information on 4 patients who had direct experience with IsaPd. These patients indicated IsaPd was effective in controlling their disease and their QoL was improved on the regimen, and the most common intolerable side effects of IsaPd included respiratory infections, anemia, and cold-like symptoms. Overall, pERC concluded that it was satisfied that IsaPd aligns with the following patient values: delays disease progression, maintains QoL, has manageable side effects, and offers an additional effective treatment option.

pERC deliberated on the cost-effectiveness of IsaPd compared with Pd alone. In discussing the results of the CADTH base case, pERC noted that the extrapolated clinical benefit expected with IsaPd over the model's time horizon compared to Pd had the greatest impact on model results. pERC noted the

uncertainty with the long-term efficacy and that the OS and PFS estimates were likely optimistic. Even under these optimistic estimates of survival for IsaPd, the ICER was far above $50,000 per QALY gained. pERC also highlighted the analyses that assessed the impact of using a discounted price of isatuximab. Even if isatuximab was offered at near zero cost, IsaPd would not be cost-effective at $50,000 per QALY gained as the price of pomalidomide remains high. pERC concluded that IsaPd is not cost-effective at a willingness-to-pay threshold of $50,000 per QALY gained even if price reductions were obtained for both isatuximab and pomalidomide.

pERC also discussed the budget impact analysis (BIA) and noted that the budget impact was substantially higher than that submitted by the sponsor. pERC noted that the factors that most influence the budget impact includes the prevalence of MM, the proportion of RRMM patients who have received prior treatment with lenalidomide and a PI, and the expected market uptake of IsaPd.

pERC deliberated on the input received from PAG regarding factors related to currently funded treatments, the eligible population, implementation factors, and the sequencing and priority of treatment. Refer to the summary table in Appendix 1 for more details.

Upon reconsideration of the Initial Recommendation, pERC reviewed the feedback received from all eligible stakeholder groups and focused its deliberation on the feedback received from the sponsor, which was the only stakeholder group that did not support early conversion of the Initial Recommendation to a Final Recommendation, and on the feedback from PAG, who disagreed with pERC on sequencing IsaPd after progression on Pd or PVd because patients with prior treatment with pomalidomide were excluded from the ICARIA-MM trial.

The sponsor's feedback primarily centred on the OS projections within the economic model. The sponsor raised concerns that the OS projections did not align with the clinical assessment and were not supported by the clinical trial evidence. pERC noted that the submitted OS data from the ICARIA-MM trial were immature and that longer follow-up of survival data would be required to reduce the extrapolation uncertainty. Although a trend was observed toward longer OS in patients receiving IsaPd compared to the Pd group within the trial, this difference between the groups was not statistically significant. pERC maintained that the CADTH reanalyses aligned with the clinical evidence given a survival benefit was predicted between IsaPd and Pd. Furthermore, the selected OS distributions in the CADTH base case reanalysis were selected based on the feedback received from clinical experts consulted by CADTH and aligned with the clinical experts' expectations that IsaPd is unlikely to provide residual survival benefits beyond disease progression. The sponsor also raised concerns regarding violation of proportional hazard assumptions in the CADTH reanalysis. However, even though the assumption of a proportional hazard is reasonable based on the clinical trial data, the assumption of a non-proportional hazard may also be reasonable. pERC considered the additional scenario analyses conducted by CADTH to explore the uncertainties in OS. These additional scenarios included assuming no survival difference upon the time point in which OS curves intersected, assuming no incremental costs or benefits would occur beyond 10 years, and/or selecting a restricted Weibull distribution. In all additional scenarios that were conducted, the ICER for IsaPd exceeded $500,000 per QALY gained compared to Pd.

A summary of pERC's deliberation related to the PAG feedback is provided in the appropriate section in Appendix 1.

EVIDENCE IN BRIEF

The CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) deliberated upon:

- a pCODR systematic review
- other literature in the Clinical Guidance Report that provided clinical context
- an evaluation of the sponsor's economic model and BIA
- guidance from the pCODR clinical and economic review panels
- input from 1 patient advocacy group: Myeloma Canada (MC)
- input from 2 registered clinician groups: Ontario Health-Cancer Care Ontario (CCO) Hematology Cancer Drug Advisory Committee (DAC), and the Canadian Myeloma Research Group (CMRG)
- input from CADTH's PAG.

Feedback on the pERC Initial Recommendation was also provided by:

- one patient advocacy group: MC
- one clinician group: CCO DAC
- CADTH's PAG
- the sponsor: Sanofi Genzyme.

The pERC Initial Recommendation was to recommend reimbursement of IsaPd in patients with RRMM who have received at least 2 prior lines of therapy including lenalidomide and a PI conditional on cost-effectiveness being improved and budget impact being addressed.

Feedback on the pERC Initial Recommendation indicated that the patient advocacy group, the registered clinician group, and the PAG all agreed with the Initial Recommendation and supported early conversion to a Final Recommendation. In their feedback, PAG requested clarification from pERC regarding sequencing of IsaPd in patients who have progressed on Pd or PVd. The sponsor agreed in part with the Initial Recommendation but did not support early conversion. The sponsor's feedback was focused on the economic evaluation of IsaPd.

OVERALL CLINICAL BENEFIT

pCODR Review Scope

The purpose of the review is to evaluate the safety and efficacy of IsaPd compared to standard of care in Canada for the treatment of patients with RRMM who have received at least 2 prior therapies including lenalidomide and a PI.

Studies Included: One international, open-label, phase III RCT

The CADTH systematic review included 1 trial, ICARIA-MM, which is an ongoing, open-label, phase III RCT that compared IsaPd to Pd alone in patients with RRMM who had received at least 2 prior lines of therapy that included lenalidomide and a PI. The trial enrolled 307 patients from 24 countries, with 154 patients randomized to IsaPd and 153 patients randomized to Pd. Randomization was stratified by number of previous lines of treatment (2 to 3 versus greater than 3) and age (< 75 versus ≥ 75 years).

Patient Populations: Adults with RRMM, median of 3 prior therapies, no prior exposure to a mAb, median age of 67, and ECOG of 0 or 1

Eligible patients in the ICARIA-MM trial included adults (18 years or older) who had a documented diagnosis of myeloma with measurable disease (by serum or urine monoclonal protein) and had failed at least 2 prior lines of anti-myeloma therapy that included a minimum of 2 consecutive cycles of lenalidomide and a PI given either alone or in combination. Treatment failure was defined as disease progression on or within 60 days after discontinuing treatment, disease progression within 6 months after achieving at minimum a partial response, or drug intolerance. All patients must have achieved a minimal response or better to at least 1 prior line of treatment; however, they were required to be refractory to their last received line of treatment. Enrolled patients had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to 2. The trial excluded patients who had primary refractory MM,

plasma cell leukemia or active amyloidosis. Prior treatment with an anti-CD38 mAb was allowed if the disease was not refractory to the treatment, and prior treatment with pomalidomide was not permitted.

For the 307 patients enrolled, the median age was 67 years, and the majority of patients were male (51.8%), White (79.5%) and had an ECOG PS of 0 or 1 (89.6%). Most patients were from Western Europe (43%) with only a small proportion of patients enrolled from North America (3.9%). The median time from initial diagnosis of MM to randomization was 4.2 years (range, 0.5 to 20.5). At study entry, most patients had either stage I (37.5%) or stage II (35.5%) disease according to the International Staging System (ISS), or stage II disease (64.2%) according to the revised International Staging System (R-ISS). All patients had relapsed and refractory disease, and the median number of previous lines of treatment was 3 (range, 2 to 11). There was 1 patient (0.3%) in the IsaPd treatment group who had received prior treatment with an anti-CD38 mAb (i.e., daratumumab).

Overall, the number of previous lines of therapy, class of drug(s) received, and refractory status to prior treatment were generally balanced between the treatment groups. The demographic and disease characteristics of patients at baseline were also balanced, though there were some notable differences noted between the 2 treatment groups. Compared to the Pd group, more patients in the IsaPd group were older (65 to 74 years: 44.2% versus 35.3%; < 65 years: 35.1% versus 45.8%), male (57.8% versus 45.8%), with ECOG PS of 1 (53.9% versus 44.4%). There was a slightly higher proportion of patients with renal impairment in the IsaPd group (38.7% versus 33.8%). More patients in the IsaPd group also had ISS stage I disease at study entry (41.6% versus 33.3%) and fewer patients had high-risk cytogenetic abnormalities (15.6% versus 23.5%).

The median duration of study treatment was longer in the IsaPd group at 41 weeks (range, 1.3 to 76.7) compared to 24 weeks (range, 1.0 to 73.7) in the Pd group. After assigned study treatment, more patients in the Pd group received subsequent systemic anti-cancer therapy (54.2%) compared to those in the IsaPd group (39.0%). Daratumumab was administered as subsequent therapy to more patients in the Pd group (29.4%) compared to the IsaPd group (3.9%).

Key efficacy results: Statistically significant improvement in PFS and ORR with IsaPd; OS data are immature

Efficacy analyses for the primary and secondary outcomes of the trial were conducted by a blinded IRC, and progressive disease was defined according to the International Myeloma Working Group (IMWG) criteria. The key efficacy outcomes deliberated on by pERC included PFS, the primary outcome, and secondary endpoints including ORR and OS, which were all part of the statistical testing hierarchy. The cut-off date for efficacy analyses was October 11, 2018, at which time the median duration of follow-up was 11.6 months.

As of the efficacy data cut-off date, the trial met its primary end point. In total, 73 patients (47.4%) in the IsaPd group and 89 patients (58.2%) in the Pd group had experienced disease progression or died, and the corresponding stratified hazard ratio (HR) for disease progression or death was 0.596 (95% confidence interval [CI], 0.44 to 0.81; P = 0.001). The median PFS was longer in the IsaPd group at 11.53 months compared to 6.47 months in the Pd group. Pre-specified subgroup analyses for PFS were consistent with the primary analysis results in the intent-to-treat population, with almost all HR estimates favouring treatment with IsaPd.

In terms of response, the ORR (i.e., PR or better as best overall response) was higher in the IsaPd group (60.4%) compared to the Pd group (35.3%). The stratified P value was < 0.0001 indicating a significant difference between the 2 groups that favoured IsaPd.

At the efficacy data cut-off date, 99 patients had died, including 43 patients (27.9%) in the IsaPd group and 56 patients (36.6%) in the Pd group. The median OS was not reached in either treatment group. The interim analysis data did not demonstrate a statistically significant difference between the 2 treatment groups, with a stratified HR of 0.687 (95% CI, 0.46 to 1.02; P = 0.0631, 1-sided significance level of 0.0008). The estimated probability of survival at 12 months was 72% and 63% in the IsaPd and Pd groups, respectively. The final analysis of OS data is planned for when 220 deaths have been observed.

Results for other efficacy end points such as time-to-progression (TTP) and duration of response (DOR) also showed favourable results for IsaPd.

Patient-reported outcomes: No clinically meaningful differences in QoL measures in either treatment group based on mean changes from baseline

PROs were measured as secondary end points in the trial. Health-related QoL was measured using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) and the accompanying Myeloma Module with 20 items (MY20); and health status utility scores used in health economic analyses were obtained through administering the EuroQol 5-Dimensions 5-Levels (EQ-5D-5L) questionnaire which included the descriptive utility system and the visual analogue scale (VAS). Questionnaires were completed on day 1 of each treatment cycle, at treatment discontinuation, and during post-treatment follow-up. Analysis of PRO end points were performed in the safety population in patients who had completed the baseline assessment plus at least 1 assessment post-baseline. The minimally important difference (MID) from baseline was defined as an increase or decrease of 10 points for EORTC QLQ-C30 and QLQ-MY20 summary scores, subscales, and symptom items; and for the EQ-5D-5L, the MID was defined as 0.074 points for the descriptive system, and 7 points for the VAS. The differences within or between groups were not assessed for statistical significance.

Overall, patient compliance for completing questionnaires was similar in each treatment group across the 3 PRO instruments; rates were high at baseline and remained at 90% or greater between cycle 2 and cycle 10. Less than half of the safety population remained and received treatment beyond cycle 6 in the Pd group and cycle 10 in the IsaPd group. Results of PROs were reported for the treatment period only.

Health-related QoL as measured by the global health status (GHS)/QoL scores of the EORTC QLQ-C30 was maintained in both treatment groups, and no clinically important mean changes in scores from baseline were observed over the treatment period. Functioning was maintained in both treatment groups and no clinically important mean changes from baseline were seen in scores for physical, role, cognitive, emotional, or social functioning in either treatment group. Similarly, symptom burden was maintained for both groups during treatment and no clinically important mean changes from baseline were seen for symptoms of fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties. There were isolated changes in symptom scores by plus or minus 10 points or more near the end of the treatment period (when sample sizes were small) for both groups; however, no consistent or clear pattern was identified. Similar results were observed for EORTC QLQ-MY20; subscale scores for body image, future perspective, disease symptoms, and side effects were maintained overall during the treatment period for both groups.

Similar to the other PROs assessed, health state utility values and VAS scores were maintained during the treatment period. There were isolated changes in scores from baseline beyond the MID threshold near the end of the treatment period, but sample sizes at these time points were small.

Safety: Overall greater toxicity with IsaPd but safety profile considered manageable

The analysis of safety outcomes was based on a data cut-off date of November 22, 2018. Compared to patients in the Pd group, patients who received IsaPd experienced more dose reductions of pomalidomide (42.8% versus 24.2%) and dexamethasone (32.9% versus 25.5%). The addition of isatuximab to pomalidomide and dexamethasone also resulted in more treatment cycle delays (57.9% versus 43.0%) as well as longer cycle delays (> 7-day delay: 34.9% versus 17.4%).

Overall, IsaPd resulted in a greater incidence of AEs. Treatment-emergent AEs (TEAEs) of any grade were reported in a similar proportion of patients, but serious TEAEs were reported in more patients treated with IsaPd and a greater proportion of patients treated with IsaPd also experienced a TEAE (all grades, serious, and severe) deemed related to at least 1 of the study drugs. The higher incidence of TEAEs in the IsaPd group did not contribute to increased discontinuation of study treatment, although individual drugs in the treatment combination were prematurely discontinued due to a TEAE in more patients compared to the Pd group (9.2% versus 2.0%).

The following TEAEs of any grade were reported at an incidence of 10% or greater, and more frequently (i.e., ≥ 5%) in patients treated with IsaPd compared to Pd: neutropenia (46.7% versus 33.6%), infusion-related reaction (36.8% versus 1.3%), upper respiratory tract infection (28.3% versus 17.4%), diarrhea (25.7% vs. 19.5%), bronchitis (23.7% vs. 8.7%), dyspnea (15.1% vs. 10.1%), nausea (15.1% vs. 9.4%), vomiting (11.8% versus 3.4%) and febrile neutropenia (11.8% versus 2.0%). Grade ≥ 3 TEAEs reported in at least 10% of patients, and more frequently (i.e., ≥ 5%) in the IsaPd group were neutropenia (46.1% versus 32.2%) and febrile neutropenia (11.8% versus 2.0%). The most common serious TEAEs (of all grades),

reported in at least 3% of patients and with a higher incidence in the IsaPd group were: urinary tract infections (3.9% versus 1.3%), neutropenia (3.3% versus 1.3%), febrile neutropenia (6.6% versus 2.0%), pathological fracture (3.3% versus 2.0%), and infusion-related reactions (3.9% versus 0.7%).

Of the TEAEs deemed related to study treatment, the most commonly reported (i.e., ≥ 10%) and with an incidence of 5% or higher in the IsaPd group were: neutropenia (42.8% versus 32.2%), infusion-related reaction (36.2% versus 0.0%), upper respiratory tract infection (9.9% versus 4.4%), and febrile neutropenia (10.5% versus 2.0%). The most commonly reported (i.e., ≥ 5%) greater than or equal to grade 3 TEAEs, with an incidence of 5% or higher in the IsaPd group were: neutropenia (42.1% versus 30.9%) and febrile neutropenia (10.5% versus 2.0%). Treatment-related serious TEAEs reported most frequently (i.e., ≥ 2%) in the IsaPd group were pneumonia (9.9%), febrile neutropenia (6.6%), infusion-related reaction (3.9%), neutropenia (2.0%), pulmonary embolism (2.0%), and thrombocytopenia (2.0%).

At the safety data cut-off date, 9 patients had died due to a TEAE: 3 patients (2.0%) in the IsaPd group and 6 patients (4.0%) in the Pd group. Fatal TEAEs were thought to be related to study treatment in 1 patient (0.7%) in the IsaPd group, due to sepsis, and 2 patients (1.3%) in the Pd group, due to pneumonia and urinary tract infection.

Limitations: Open-label design and immature OS data

Overall, the ICARIA-MM trial was well-designed; however, there were some limitations that should be considered when interpreting the results, which include the following:

- Due to the open-label study design, the investigators and patients were aware of treatment allocation. It is possible that due to their knowledge of assigned treatment, the trial results may be at risk for biases related to the lack of blinding that can affect the measurement and reporting of outcomes, potentially biasing results in favour of the IsaPd group. This bias is more relevant to the reporting of subjective outcomes (e.g., adverse effects, patient-reported symptoms, and outcomes) by the patients and care providers than efficacy end points, since efficacy outcomes were measured by blinded IRC to reduce investigator bias.
- During the study follow-up period, patients were permitted to receive subsequent treatment for RRMM, which included daratumumab, lenalidomide, and PIs. The decision to administer subsequent treatment after disease progression and the choice of treatment was up to the investigator's discretion. In an unblinded trial setting, the choice of subsequent therapy may be influenced by the treatment received in the study. The impact of this bias is unknown; however, overall, a higher proportion of patients randomized to the control group received subsequent therapy (39.0% Isa Pd versus 54.2% Pd) and this may confound the assessment of OS by prolonging survival beyond what would have occurred strictly with study treatment and overestimating survival benefit. Furthermore, the subsequent use of mAb therapy (i.e., daratumumab) was higher in the Pd group. The higher proportion of patients receiving subsequent treatment in the Pd group would be expected to favour the Pd group.
- The final analysis of OS is scheduled after 220 deaths have occurred in the trial. At the interim analysis, a total of 99 deaths had occurred by the data cut-off date, corresponding to a 45% information fraction. At that time the median survival was not reached in either treatment group. Although there was a non-statistically significant trend toward longer OS in patients randomized to IsaPd, current OS data are immature; therefore, longer follow-up of survival data is required to appropriately characterize the long-term effects of adding isatuximab to pomalidomide and dexamethasone.
- To account for interim analyses as well as key secondary end points, the overall type I error rate was appropriately controlled using a closed test procedure. However, there were several pre-specified subgroup analyses and secondary outcomes (i.e., TTP, DOR, PROs) assessed in the trial that were not part of the statistical testing hierarchy and therefore these results were not adjusted to account for multiple comparison testing to control the risk of type I error. These results should be considered as supplemental to the primary and key secondary end points and be interpreted with caution.
- Hematologic abnormalities, such as neutropenia and thrombocytopenia, were captured as laboratory results and as reports from investigators. However, only serious hematologic AEs or those which led to study treatment modification or discontinuation were documented as an AE (i.e., only those deemed clinically significant by the investigators) in the trial. As result, investigator bias could result in the underreporting of hematologic AEs.

Comparator information: ITC of IsaPd versus Kd

In the absence of direct evidence comparing IsaPd to Kd for the treatment of patients with RRMM who have been exposed to 2 prior therapies (including lenalidomide and a PI), the sponsor submitted an unadjusted and unanchored ITC comparing the 2 treatments in this patient population. Two trials were included in the ITC: the ICARIA-MM trial provided individual patient-level data for IsaPd, and the ENDEAVOR trial provided aggregate data for Kd in the analysis of OS and published median values were used in the analysis of PFS. Although statistical comparisons between the treatments were provided for these key outcomes (OS HR = 1.0, 95% CI, 0.67 to 1.62, P = 0.848; PFS HR = 0.75, 95% CI, 0.52 to 1.07, P = 0.11), inherent limitations to the unanchored and unadjusted approach used in the ITC introduces a high level of uncertainty in the results. The estimated HRs generated by the ITC suggested no difference in OS and PFS between the 2 treatments. The heterogeneity in the patient populations of the 2 trials, particularly surrounding important treatment effect modifiers relating to prior treatment history (i.e., number and types of prior lines of therapy received) and prognostic factors have the potential to severely bias and limit the generalizability of the results. As such, no conclusions can be made regarding the comparative efficacy of IsaPd and Kd based on the submitted ITC, and its results should be interpreted with caution.

Need and Burden of Illness: Incurable neoplasm requiring effective treatment choices

Symptomatic MM (MM that necessitates treatment) is an incurable plasma cell neoplasm that represents 1.5% of all new cancers in Canada with an estimated 3,400 new cases annually and accounts for approximately 10% of all hematologic malignancies. MM largely affects older adults with the average age at diagnosis being 62 years for men and 61 years for women; only 4% of cases are diagnosed in individuals under the age of 45. In Canada, the 5-year net survival rate for symptomatic MM is 44%. Patients with symptomatic MM can be stratified into groups with differing prognoses based on clinical and laboratory parameters that include high-risk cytogenetic features [i.e., FISH-detected t(4;14), t(14;16), t(14;20), del(17p), or gain(1q); non-hyperdiploid karyotype; high-risk gene expression profile signature; and del(13)]. In addition to cytogenetic risk factors, 2 other clinical features that are also associated with aggressive disease biology are elevated serum lactate dehydrogenase (LDH), and evidence of circulating plasma cells on routine peripheral smear examination. To date, there has not been definitive evidence from randomized trials that has identified a superior treatment strategy that differs based on patient risk stratification.

Regardless of the choice and duration of initial therapy, most patients with MM will eventually relapse. The goal of therapy for patients with RRMM is to achieve disease control with acceptable toxicity and patient defined QoL. Outside of clinical trials where provincial funding is available, the current treatment options for patients with RRMM include DVd or DRd, Pd with or without cyclophosphamide, as well as Kd. The treatments available to patients are complex and dependent on several factors that include prior therapies and response, side effects, patient comorbidities/frailty, individual preferences, and public funding. While the optimal sequencing of myeloma therapies remains unclear, the opportunity to provide patients with more options and choice for therapy in an incurable disease is critical, from both a survival and psychosocial perspective.

Registered Clinician Input: IsaPd has efficacy and good tolerability, and fills unmet need in patients who are ineligible for publicly funded daratumumab

Two registered clinician inputs were provided on behalf of 2 clinicians from the CCO Hematology DAC and 15 clinicians from CMRG for the review of IsaPd for the treatment of RRMM in patients who have received at least 2 prior therapies including lenalidomide and a PI. Both clinician groups cited Pd and Kd as currently available treatments for RRMM in Canada, and that cyclophosphamide can be added to Pd treatment. In both inputs it was highlighted that in most provinces patients whose disease is refractory to both lenalidomide and bortezomib are not eligible for publicly funded daratumumab.

CCO and CMRG clinicians considered the eligibility criteria of the ICARIA-MM trial to be reasonable and applicable to Canadian clinical practice; however, both groups indicated that there should not be restrictions based on renal function or blood counts. Unlike the trial, in clinical practice the clinicians noted there is no requirement for patients to have measurable myeloma markers or less than grade 1 prior toxicity. Clinicians stated that IsaPd offers favourable efficacy with a low rate of treatment-related AEs leading to treatment discontinuation and is a regimen that has good tolerability and can be used in patients with renal insufficiency. The clinicians indicated that the potential harms of the combination include the contraindication of a prior severe rash with lenalidomide, as there may exist some cross-

reactivity with pomalidomide; and patients with a prior history of frequent sinopulmonary infections requiring antibiotics may be at higher risk of developing upper respiratory tract infections that may warrant additional precautions at the time of initiation of IsaPd.

Both clinician groups indicated that IsaPd is a potentially important therapy for a particular patient group with significant unmet need: patients whose disease has progressed after both bortezomib and lenalidomide treatment and are ineligible for daratumumab. The clinicians from CMRG noted that IsaPd yields a PFS benefit in lenalidomide-refractory patients; and in Ontario, these patients do not currently have any funded access to an anti-CD38 mAb and are currently ineligible for new immunotherapy treatments available through clinical trials. The clinicians also stated that currently there is a relatively small proportion of Canadian patients on lenalidomide plus bortezomib and dexamethasone (RVd) for RRMM, and patients who receive DVd until progression would not be eligible for IsaPd as a third-line therapy. Therefore, access to IsaPd at next progression would be important for patients not previously treated with daratumumab. The clinicians stated that for patients currently on Pd (+/- cyclophosphamide) who have not experienced disease progression, the addition of isatuximab, if not otherwise previously treated with daratumumab, would be optimal. Accordingly, the clinicians predicted that should IsaPd be reimbursed it would most likely replace Pd, Pd in combination with cyclophosphamide, and Kd due to the inability of using both pomalidomide and carfilzomib in the same patient.

PATIENT-BASED VALUES

Values of patients with RRMM: Disease symptoms have physical and social impacts that affect QoL, and have financial implications

One patient group, MC, provided input on isatuximab for the treatment of RRMM in patients who have received at least 2 prior therapies that included lenalidomide and a PI. MC obtained the input from a total of 329 Canadian patients through several patient surveys conducted in June and July 2020. From the patient perspective, infections, kidney problems, and pain were the most common symptoms of MM, and mobility, neuropathy, shortness of breath, and fatigue were reported to largely impact the daily lives of patients and their overall QoL. In addition to physical symptoms, patients indicated that MM also affects QoL by having a significant impact on work life, travel, and the ability to exercise and volunteer. MC indicated that living with MM has many financial implications for patients that include drug costs, loss of income due to absence from work, and parking costs for medical appointments. Most patients surveyed (60%) had received at least 2 prior lines of therapies including lenalidomide and bortezomib, carfilzomib, or ixazomib; and some patients (14%) had used or were using Pd.

Patient values on treatment: Improved QoL, effective treatments with fewer side effects, and availability of multiple effective treatments that offer patient choice.

Patient respondents indicated that they value effective treatments for MM that offer disease control or remission with fewer side effects. Although patients indicated they wanted to avoid all side effects of treatment, they cited confusion, infection, and pain as the symptoms they most wanted to avoid. Patients desire treatment options for MM that improve their overall QoL and emphasized the importance of choice among various effective treatment options to improve patient prognosis. Patients currently receiving daratumumab indicated they would like to have access to this treatment regimen in the event of relapse. Six patient respondents reported they had direct experience with IsaPd. These patients reported their QoL was improved on that regimen and that it was effective in controlling their disease. According to patients, the most common intolerable side effects of IsaPd included respiratory infections, anemia, and cold-like symptoms.

ECONOMIC EVALUATION

Isatuximab is supplied as a 100 mg or 500 mg single-use vial. The recommended dose for isatuximab is 10 mg/kg body weight given as an IV injection, weekly in the first treatment cycle, and bi-weekly in subsequent treatment cycles, in combination with standard doses of pomalidomide plus dexamethasone (IsaPd) until disease progression or unacceptable toxicity. Pre-medications (e.g., dexamethasone, acetaminophen, H2 antagonists, diphenhydramine) should be given before the administration of isatuximab. At the sponsor-submitted price of $758 per 100 mg and $3,789 per 500 mg vials for isatuximab, the total drug acquisition cost of isatuximab is $21,221 in the first treatment cycle and

$10,611 in subsequent treatment cycles; and the total cost of IsaPd is $31,727 to $31,733 in the first treatment cycle and $21,117 to $21,123 in subsequent cycles.

The sponsor submitted a cost-utility analysis based on a partition-survival model evaluating IsaPd compared to Pd, for patients with relapsed and/or refractory MM. Costs and quality-adjusted life-years were modelled over a lifetime time horizon (20 years) from the perspective of the publicly funded health care payer. The proportion of patients who were progression-free, experienced progressive disease, or were dead at any time over the model's time horizon was derived from non-mutually exclusive survival curves. Progression was defined according to the IMWG response criteria. Clinical efficacy was based on data from the ICARIA-MM trial and extrapolated by parametric survival analysis.

CADTH identified the following key limitations with the sponsor's pharmacoeconomic analysis:

- Relevant comparators such as Pd with cyclophosphamide, and Kd were excluded from the sponsor's base case. Although the sponsor provided a scenario analysis comparing IsaPd to Kd, the comparative clinical efficacy was informed by an adjusted and unanchored ITC with several limitations.
- There was uncertainty regarding the long-term extrapolation of the OS and PFS data beyond the observed trial period for IsaPd and Pd. OS data were immature as median OS was not reached in the observed period. The sponsor's chosen extrapolated curves for IsaPd and Pd provided optimistic and clinically implausible projections. This led to uncertainty with the extrapolation of the observed data within the model, particularly given that much of the benefit observed with IsaPd occurred over the extrapolation period.
- Health state utilities applied within the model lacked face validity and the inclusion of treatment-specific utilities in effect double-counted the disutility associated with AEs.
- Total drug acquisition costs of IsaPd and Pd may have been overestimated due to the sponsor's choice of the time-to-treatment discontinuation (TTD) parametric curve according to the clinical experts consulted on this review.
- The proportion of patients who would receive subsequent therapy in the economic model did not align with expectations in clinical practice according to the clinical experts consulted.

CADTH addressed some of the identified limitations by undertaking the following reanalyses: selecting the Weibull distribution for the OS of IsaPd and Pd; selecting the Gompertz distribution for PFS and TTD of IsaPd; selecting the Weibull distribution for PFS and TTD of Pd; and, revising the utility values for PFS and progressed disease health states. Based on these revisions, the results of the CADTH reanalyses were consistent with the overall findings of the sponsor: IsaPd is not cost-effective at a willingness-to-pay threshold of $50,000 per QALY gained. The ICER for IsaPd versus Pd was $1,555,947 per QALY gained in the CADTH base case.

The results were primarily driven by the increased acquisition cost of isatuximab and the expected incremental clinical benefit with isatuximab over the model time horizon for IsaPd compared to Pd. Price reduction analyses suggest that, even if isatuximab was offered at zero cost, IsaPd would not be cost-effective at a $50,000 per QALY threshold as the price of pomalidomide remains high. A 98% price reduction for isatuximab combined with a 50% price reduction for pomalidomide would be needed for IsaPd to be considered cost-effective at a $50,000 per QALY threshold.

Overall, it is highly unlikely that IsaPd would be considered a cost-effective use of Canadian health care resources at a $50,000 per QALY gained threshold, even if price reductions were obtained for both isatuximab and pomalidomide.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact:

CADTH identified the following key limitations with the sponsor's analysis: assumption that IsaPd would be used as a second-line treatment option for the indicated population; uncertainty with several

epidemiological inputs used to estimate the market size; and the market share of treatments in the reference and new drug scenarios did not reflect clinical experts' expectations. CADTH removed IsaPd use as a second-line treatment, revised parameters used to estimate the market size, and corrected the market shares of IsaPd, Pd, and Kd. Together, these revisions suggest the total budget impact was underestimated. Uncertainty still remains with the potential market uptake of IsaPd. Should the market uptake be greater than anticipated, the budget impact of IsaPd may be underestimated.

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee

Recommendations are made by the CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) following the pERC *Deliberative Framework*. pERC members and their roles are as follows:

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice-Chair)
Daryl Bell, Patient Member
Dr. Jennifer Bell, Bioethicist
Dr. Kelvin Chan, Oncologist
Dr. Michael Crump, Oncologist
Dr. Matthew Cheung, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist*
Dr. Christine Kennedy, Family Physician
Dr. Christian Kollmannsberger, Oncologist
Dr. Christopher Longo, Health Economist
Cameron Lane, Patient Member
Valerie McDonald, Patient Member
Dr. Marianne Taylor, Oncologist
Dr. W. Dominika Wranik, Health Economist

*No longer a member of the CADTH pERC.

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

- Dr. Maureen Trudeau who did not vote due to her role as pERC Chair.

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

- Dr. Maureen Trudeau, who did not vote due to her role as pERC Chair.

Avoidance of conflicts of interest

All members of the CADTH 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 CADTH website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of isatuximab for RRMM, through their declarations, there were no members who had a real, potential, or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, no member 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 CADTH website. Please refer to the pCODR Guidance Reports for more detail on their content.

Consulting publicly disclosed information

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

Use of this Recommendation

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Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

APPENDIX 1: CADTH pERC RESPONSES TO PAG IMPLEMENTATION QUESTIONS

PAG implementation questions	pERC Recommendation
Patient population	
• In view of the characteristics of the patient population and exclusion criteria in the ICARIA-MM trial, PAG is seeking clarity on whether the following patients would be eligible for treatment with IsaPd:	
○ Patients with ECOG performance status greater than 2	○ pERC agreed with the CGP that patients with an ECOG performance status greater than 2 may benefit from IsaPd and therefore eligibility should be determined for patients on an individual basis.
○ Patients with primary amyloidosis	○ pERC noted that the ICARIA-MM trial excluded patients with primary amyloidosis. pERC agreed with the CGP that in the absence of data, IsaPd should not be used in these patients.
○ Patients with primary refractory MM	○ pERC noted that the ICARIA-MM trial excluded patients with primary refractory MM, which was defined in the trial as patients who had never achieved at least a minimal response with any treatment. pERC discussed that the small number of patients with primary refractory MM are among the highest risk patients in terms of prognosis, and currently available treatments for this subgroup are extremely limited and often include palliative therapies. Considering these factors, pERC agreed with the CGP that otherwise eligible patients with primary refractory MM could be considered for treatment with IsaPd.
○ Patients with free light chain measurable disease only	○ The CGP indicated that light chain myeloma can be measured with serum free light chain assays, and that this subtype of myeloma is routinely managed in the same manner as other subtypes of myeloma. pERC therefore agreed with the CGP that patients with this subtype of myeloma should be eligible for IsaPd.
• PAG also seeks information on: ○ Whether patients with high-risk cytogenetics exhibit a distinct response to IsaPd and should be treated differently	○ pERC noted that patients with known high-risk cytogenetics [del(17p), t(4;14), or t(14;16) by FISH] comprised a notable proportion of patients in the ICARIA-MM trial and pre-specified subgroup analysis results demonstrated that they respond equally well to IsaPd when compared to patients without high-risk cytogenetics. Based on this evidence, pERC agreed that IsaPd should be offered to patients with high-risk cytogenetics that otherwise fit the ICARIA-MM trial eligibility criteria.
○ PAG identified a potential time-limited need for patients currently on Pd or Kd who have not progressed, and seeks guidance on whether they could be switched to IsaPd, adding isatuximab in the case of patients on Pd. In the latter scenario, PAG would like to know if a switch from Pd plus bortezomib (PVd) could also be allowed.	○ pERC agreed with the CGP that patients currently on Pd who have not progressed and meet the ICARIA-MM trial eligibility criteria could have isatuximab added to this regimen since this would be consistent with the approach taken for other myeloma regimens. For patients currently on Pd, Kd or PVd who meet the trial eligibility criteria, pERC agreed that IsaPd could be considered upon progression or intolerance to Pd, Kd or PVd.

	○ PAG disagreed with sequencing IsaPd after progression on Pd or PVd because patients with prior treatment with pomalidomide were excluded from the ICARIA-MM trial: pERC discussed that the ICARIA-MM trial excluded patients who received prior pomalidomide and therefore there are no data from the trial to address sequencing IsaPd after progression on Pd or PVd. However, pERC acknowledged that there is an unmet need for patients who have never received an anti-CD38 therapy despite having received pomalidomide. pERC agreed with the CGP that this is a small patient population that is likely to decrease over time. pERC agreed that these patients should have access to an anti-CD38 therapy as a time-limited need and therefore be considered for treatment with IsaPd assuming they otherwise meet the criteria for the ICARIA-MM trial.
Implementation factors	
• PAG is seeking guidance on treatment duration and discontinuation criteria	• pERC agreed that treatment with IsaPd should follow the ICARIA-MM trial protocol and be continued until there is clear evidence of progression as per IMWG criteria and/or unacceptable toxicity. However, the CGP noted that it is currently unclear whether treatment should be continued beyond biochemical progression in the absence of clinical progression. pERC agreed with the CGP that in clinical practice it is reasonable and not uncommon to allow patients to continue treatment in the absence of clinical progression, but that this decision should be determined for patients on an individual basis.
• PAG noted that the IMWG consensus criteria indicate that response or progressive disease require confirmation with 2 consecutive readings of the applicable disease parameter using 2 discrete samples. PAG is seeking guidance on whether this should be required in clinical practice.	• pERC agreed that 2 consecutive readings should be performed as per IMWG consensus criteria; however, they also agreed with the CGP that the determination of disease progression that requires a change in current therapy should not solely be based on biochemical progression alone and should also consider other patient factors that includes clinical progression.
• PAG also seeks advice on the addition of cyclophosphamide upon biochemical progression	• There are no data from the ICARIA-MM trial to support the addition of cyclophosphamide to IsaPd upon biochemical progression. However, the CGP noted that it is reasonable for the clinician/patient to consider the addition of cyclophosphamide as a bridging therapy to the subsequent line of therapy. pERC agreed with CGP that the approach of adding cyclophosphamide is a low cost and low-risk treatment option that should be available to patients on an individual basis. pERC noted that the budget impact may be underestimated under these circumstances given it was not considered within the economic analyses.
• PAG seeks guidance on dose reduction for isatuximab to mitigate infusion reactions, given dose modifications were not permitted in the trial	• pERC agreed with the CGP that dose reduction should not be used as a primary strategy to mitigate infusion reactions as this may lead to decreased efficacy of isatuximab. Instead, other strategies such as the use of antihistamines, steroids, and slowing the infusion time should be used.

Sequencing and priority of treatments	
• PAG is seeking to confirm the place in therapy of IsaPd and sequencing with other regimens for MM, including the scenarios below:	
○ Overall optimal sequence of therapies that should be given before IsaPd	• pERC agreed with the CGP that the optimal sequence of therapies for MM remains unknown and is difficult to determine since treatment is individualized based on patient and disease factors, provincial funding of regimens, and evolving therapy options.
○ Patient factors justifying preferential use of IsaPd over Pd or Kd in the third-line setting	• pERC agreed with the CGP that there are no specific patient factors that justify the preferential use of Pd or Kd in the third-line setting; however, it is reasonable to consider not using Kd in patients with significant history of cardiopulmonary dysfunction and neuropathy.
○ Use of IsaPd after first-line RVd and no other prior line of therapy (would this be considered off-label?)	• pERC agreed that this patient population would not be eligible for IsaPd according to the ICARIA-MM trial eligibility criteria (i.e., due to less than two prior lines of therapy). However, pERC agreed with the CGP that IsaPd should be considered for patients resistant and refractory to lenalidomide and bortezomib who have no prior exposure to an anti-CD38 mAb therapy, regardless of the line of therapy. pERC considered that this patient population is likely to be small and would otherwise be unable to receive a mAb since they are ineligible for daratumumab as second-line treatment.
○ If RVd was used in first-line therapy, what second-line therapies can be given before patients are considered eligible to IsaPd?	• The CGP noted it is unknown whether it is preferable to use Kd before or after IsaPd. pERC agreed with the CGP that the timing of its use should be at the discretion of the treating physician and based on individual patient need.
○ Evidence on the use of isatuximab after failure of any daratumumab-containing therapy	• pERC noted that the ICARIA-MM trial excluded patients who were refractory to previous therapy with an anti-CD38 mAb. Therefore, there is no evidence on the efficacy of isatuximab after failure of any daratumumab-containing therapy.
○ Using IsaPd in patients who discontinued daratumumab in a prior line of therapy without evidence of progression, if all other eligibility criteria are met	• pERC agreed with the CGP that it would be clinically reasonable to use IsaPd in patients who discontinued daratumumab before disease progression or due to intolerance. pERC noted that the ICARIA-MM trial enrolled 1 patient in the IsaPd treatment group who had previously been given daratumumab.
○ Evidence on the use of isatuximab after carfilzomib-containing regimens in the RRMM setting	• pERC noted that 25% of patients in the ICARIA-MM trial had previously received carfilzomib. pERC agreed with the CGP that data from the trial suggest that using IsaPd after carfilzomib offers a clinical benefit.
○ Addition of isatuximab to Pd upon biochemical progression on the latter	• pERC noted that the ICARIA-MM trial did not enroll patients who had biochemical progression on Pd. pERC agreed with the CGP that it would be reasonable to consider the addition of isatuximab in patients who are mAb naive in an effort to better control disease, and that this approach should be considered in patients on an individual basis.

○ Options after failure of IsaPd	• pERC agreed with the CGP that treatment options to consider after failure on IsaPd could include a carfilzomib-containing regimen if not already received, compassionate access to Selinexor or belantamab, a clinical trial, or palliation with steroids/cyclophosphamide.
○ Continued use of isatuximab plus dexamethasone in cases of pomalidomide intolerance or discontinuation	• pERC agreed with the CGP that the continued use of isatuximab would be considered in cases of intolerance or discontinuation of pomalidomide as this approach is consistent with clinical practice, especially in individual patients where there is evidence of a biochemical and/or clinical response.

ASCT = autologous stem cell transplant; CGP = Clinical Guidance Panel; IsaPd = isatuximab plus pomalidomide plus dexamethasone; ECOG = Eastern Cooperative Oncology Group; IMWG = International Myeloma Working Group; Kd = carfilzomib plus dexamethasone; mAb = monoclonal antibody; MM = multiple myeloma; PAG = Provincial Advisory Group; Pd = pomalidomide plus dexamethasone; pERC = CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee; PR = partial response; PVd = pomalidomide plus bortezomib plus dexamethasone; RRMM = relapsed/refractory multiple myeloma; RVd = lenalidomide plus bortezomib plus dexamethasone.