

CADTH Reimbursement Recommendation

Isatuximab (Sarclisa)

Indication: In combination with carfilzomib and dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma who have received 1 to 3 prior lines of therapy

Sponsor: Sanofi Genzyme, a division of Sanofi-Aventis Canada Inc.

Final recommendation: Reimburse with conditions

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What Is the CADTH Reimbursement Recommendation for Sarclisa?

CADTH recommends that Sarclisa be reimbursed by public drug plans for the treatment of relapsed or refractory multiple myeloma (MM) if certain conditions are met.

Which Patients Are Eligible for Coverage?

Sarclisa should only be covered for adult patients who have relapsed or refractory MM and who have received 1 to 3 prior treatments. Patients should show the presence of a marker called M protein in their blood or in urine and have good Performance Status. Patients must not have already had treatment with an anti-CD38 monoclonal antibody (mAb) (a type of drug that includes Sarclisa and similar medications), must not be resistant to treatment with carfilzomib (another drug used for MM), and must have acceptable heart function. To be effective, Sarclisa should be combined with carfilzomib and dexamethasone.

What Are the Conditions for Reimbursement?

Sarclisa should only be reimbursed if it is prescribed by physicians with expertise and experience in managing MM and if the cost of Sarclisa is reduced.

Why Did CADTH Make This Recommendation?

- Evidence from a clinical trial suggested that Sarclisa delayed progression of MM when added to a commonly used regimen of 2 other drugs for multiple myeloma.
- Sarclisa meets patient needs of improving disease control by achieving longer remission and by having manageable side effects.
- Based on CADTH's assessment of the health economic evidence, Sarclisa does not represent good value to the health care system at the public list price. A 100% price reduction of Sarclisa is not sufficient to achieve good value unless the price plans pay for carfilzomib, which has to be given in combination with Sarclisa, is also 61% lower than its list price.
- Over 3 years Sarclisa is expected to increase drug costs to the public drug plans by more than \$117,000,000.

Additional Information

What is Multiple Myeloma?

MM is a cancer of plasma cells (the white blood cells that make antibodies) that is more common in older adults and accounts for 10% to 15% of all blood cancers. Many patients do not respond to initial treatments and their disease will relapse, so they will need to try many different treatments.

Unmet Needs in Multiple Myeloma

Treatments that are better at controlling disease and are less toxic are needed. There is a particular need for patients who are resistant to treatment as prognosis tends to be poor in these patients.

How Much Does Sarclisa Cost?

Treatment with Sarclisa is expected to cost approximately \$12,126 per 28-day cycle (initial cycle = \$24,253). When used in combination with carfilzomib and dexamethasone, treatment is expected to cost \$27,472 per 28-day cycle (initial cycle = \$36,532).

Recommendation

The CADTH pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommends that isatuximab combined with carfilzomib and dexamethasone (IsaKd) be reimbursed for the treatment of adult patients with relapsed or refractory MM who have received 1 to 3 prior lines of therapy only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One open-label, phase III superiority trial (IKEMA; N = 302) demonstrated that treatment with IsaKd resulted in added clinical benefit when compared to carfilzomib and dexamethasone (Kd) in patients with relapsed or refractory MM who had been previously treated with 1 to 3 prior regimens. At the interim analysis, the IKEMA trial showed a statistically significant and clinically meaningful improvement in progression-free survival (PFS) with IsaKd compared to Kd (hazard ratio [HR] = 0.53; 99% confidence interval [CI], 0.318 to 0.889; P = 0.0007). The PFS benefit was consistent across patient subgroups, including patients who had relapsed on or were refractory to immunomodulating agents (IMiDs) and/or proteasome inhibitors (PIs), those who had prior autologous stem cell transplant, and those who had received more than 1 line of prior therapy. Overall survival (OS) data were immature and were not compared at the interim analysis. Health-related quality of life (HRQoL) was assessed but not formally compared between the treatment groups in the trial; however, the available evidence suggested that HRQoL was maintained over time in the IsaKd group. The incidence of adverse events (AEs) was similar between the treatment groups, although there were more infusion reactions and more infections, particularly pneumonia, in the IsaKd group. Despite these increases, pERC considered the safety profile of IsaKd to be manageable.

MM is an incurable disease and pERC agreed that there is an unmet need for additional effective treatments in the relapsed and refractory setting, particularly for patients who are refractory to IMiDs and PIs. Patients identified a need for new and effective treatments that control disease, prolong remission, and improve quality of life with fewer side effects than currently available treatments. Given the totality of the evidence, pERC concluded that IsaKd meets some of these needs by improving disease control, which results in longer remission, and having manageable side effects. pERC was unable to draw definitive conclusions on the effect of IsaKd on patients' quality of life due to limitations of the evidence.

Owing to limitations with the sponsor's modelling approach and the lack of informative comparative data to regimens currently considered standard of care for this patient population in Canada, a base-case estimate of cost-effectiveness was unable to be determined in the Health Canada-approved indication. CADTH conducted an exploratory reanalysis and determined that the incremental cost-effectiveness ratio was likely close to \$1,588,632 per quality-adjusted life-year (QALY) compared to Kd; therefore, IsaKd is not cost-effective at a \$50,000 per QALY willingness-to-pay threshold. CADTH notes that this estimate may underestimate the true incremental cost-effectiveness ratio due to favourable modelling assumptions, as well as the absence of lower cost comparators that could not be considered in the analysis. Based on the exploratory analysis, a 100% price reduction for isatuximab is not sufficient to achieve cost-effectiveness at a \$50,000 per QALY threshold unless the price paid by public plans for carfilzomib is also 61% lower than its list price.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason
Initiation	
<p>1. Treatment with IsaKd should only be initiated in adult (≥ 18 years) patients with relapsed or refractory MM who meet all of the following criteria:</p> <ul style="list-style-type: none"> 1.1. measurable disease defined as serum M protein of at least 0.5 g/dL and/or urine M protein of at least 200 mg per 24 hours 1.2. received at least 1 prior line of therapy. 	<p>Evidence from the IKEMA trial demonstrated that treatment with IsaKd had superior PFS in patients with relapsed or refractory MM who had measurable disease and had received at least 1 prior treatment regimen.</p>
<p>2. Patients should have good Performance Status.</p>	<p>The IKEMA trial enrolled patients with an ECOG Performance Status of ≤ 2. It is recognized that Performance Status may be related to underlying disease; therefore, for some patients, an improvement in status is expected after initiation of treatment. As such, clinicians could consider using IsaKd in patients with an ECOG Performance Status > 2 at their discretion.</p>
<p>3. Patients must not:</p> <ul style="list-style-type: none"> 3.1. have had prior treatment with an anti-CD38 mAb 3.2. been refractory to carfilzomib 3.3. have left ventricular ejection fraction $< 40\%$. 	<p>The IKEMA trial included patients who had previous treatment with but were not refractory to an anti-CD38 mAb. However, only 5 patients in the IsaKd treatment group had prior exposure to an mAb, of whom 1 had received daratumumab. Therefore, there is no robust evidence from the trial on the efficacy of IsaKd in eligible patients who have received at least 1 prior line of therapy that includes an anti-CD38 mAb.</p> <p>The CADTH review identified no evidence to demonstrate a treatment benefit for IsaKd in patients who are refractory to carfilzomib or who have a ventricular ejection fraction $< 40\%$ as these patients were excluded from the IKEMA trial.</p>
Discontinuation	
<p>4. Treatment with IsaKd should be discontinued upon occurrence of any of the following:</p> <ul style="list-style-type: none"> 4.1. evidence of disease progression according to IMWG criteria 4.2. unacceptable toxicity despite dose modification. 	<p>In the IKEMA trial, disease assessments were performed every treatment cycle in accordance with IMWG criteria. According to clinician input, in clinical practice, patients would be assessed for response and progression every 1 to 3 months.</p> <p>Treatment with IsaKd continued until disease progression or unacceptable toxicity. No evidence was identified that showed effectiveness when continuing treatment with IsaKd in patients whose disease has progressed.</p> <p>Dose modification or delay for toxicity was permitted in the IKEMA trial. If intolerable side effects could not be managed with appropriate dose modification or delay, treatment with IsaKd was discontinued. If one of the study drugs was discontinued, patients could continue with the other drugs in the regimen until disease progression or unacceptable toxicity occurs.</p>

Reimbursement condition	Reason
Prescribing	
5. IsaKd should only be prescribed by clinicians with expertise and experience in the management of patients with MM and can be administered in a variety of settings that include hospital outpatient clinics, community clinics, and IV oncology drug administration facilities.	To ensure that IsaKd is prescribed only for appropriate patients, and that adverse effects are managed in an optimized and timely manner.
Pricing	
6. A reduction in price	<p>CADTH undertook a price reduction analysis based on an exploratory reanalysis that used appropriate assumptions regarding drug cost and clinically plausible assumptions for the efficacy of IsaKd vs. Kd. A 100% price reduction of isatuximab is not sufficient to achieve cost-effectiveness at a \$50,000 per QALY threshold unless the price public plans pay for carfilzomib is also 61% lower than its list price.</p> <p>Even if the price paid for carfilzomib was substantially lower (90% lower than the list price) an 85% price reduction for isatuximab would be needed for the IsaKd regimen to achieve cost-effectiveness at a \$50,000 per QALY.</p> <p>Cost-effectiveness relative to other treatment regimens is unknown though CADTH notes that with a 100% price reduction to isatuximab, IsaKd remains more costly over the full course of therapy than most other regimens, such as Dvd.</p>
Feasibility of adoption	
7. The feasibility of adopting IsaKd must be addressed.	At the submitted price, the budget impact of reimbursing IsaKd is expected to be greater than \$40 million in year 3.

Dvd = daratumumab plus bortezomib and dexamethasone; ECOG = Eastern Cooperative Oncology Group; IMWG = International Myeloma Working Group; IsaKd = isatuximab plus carfilzomib and dexamethasone; Kd = carfilzomib and dexamethasone; mAb = monoclonal antibody; MM = multiple myeloma; PFS = progression-free survival; QALY = quality-adjusted life-year; vs. = versus.

Implementation Guidance

Issues that may impact the drug plans' ability to implement a recommendation as identified by pERC and the drug programs are summarized in Table 2.

Table 2: Implementation Guidance From pERC

Condition number in Table 1	Implementation considerations and guidance
1	The IKEMA trial excluded patients who had primary refractory MM, serum-free light chain measurable disease only, known amyloidosis concomitant with MM, and plasma cell leukemia, as well as patients who had received > 3 prior lines of therapy. pERC agreed with the clinical experts that these patients are likely to benefit from treatment with IsaKd and therefore should also be eligible for treatment reimbursement.

Condition number in Table 1	Implementation considerations and guidance
7	<p>In the IKEMA trial, carfilzomib was administered intravenously at 20 mg/m² on days 1 and 2 of cycle 1; 56 mg/m² on days 8, 9, 15, and 16 of cycle 1; and then 56 mg/m² on days 1, 2, 8, 9, 15, and 16 of subsequent cycles.</p> <p>There is interest among clinicians to use weekly dosing of carfilzomib with dexamethasone to decrease chemotherapy chair time and potentially decrease the toxicity associated with carfilzomib. The clinical experts indicated that this approach is being used in Canadian clinical practice based on supporting evidence. pERC agreed that a weekly dosing schedule of carfilzomib could be considered with the IsaKd regimen.</p>

IsaKd = isatuximab plus carfilzomib and dexamethasone; MM = multiple myeloma; pERC = pan-Canadian Oncology Drug Review Expert Review Committee.

Discussion Points

- MM is an incurable, relapsing-remitting cancer that is associated with significant impairment to patients' quality of life as a result of both the disease and the toxicities of treatment. In patients with relapsed or refractory MM, the sequencing of treatments is primarily dictated by what regimens patients have received in prior lines and what is publicly funded in their jurisdiction. pERC acknowledged the need for new and effective treatments, especially for patients who become refractory to lenalidomide and require a subsequent regimen without this drug, preferably one that includes a different mechanism of action. Clinician input highlighted the need for patients who have relapsed to have access to a CD38 mAb as early as possible because most patients in Canada do not receive one as part of their first-line regimen.
- pERC discussed the results of the IKEMA trial that demonstrated that IsaKd had superior and clinically meaningful treatment benefit compared to Kd in terms of PFS at the interim analysis. The PFS benefit was consistent among important subgroups of patients, including those who had relapsed on or were refractory to IMiDs and/or PIs, those who had prior autologous stem cell transplant, and those who had received more than 1 line of prior therapy. pERC agreed with patient and clinical expert input that PFS is a meaningful end point in this patient population. The PFS results were observed despite there being no statistically significant difference in objective response rate (ORR) between the treatment groups. pERC noted that the early failure of the statistical testing hierarchy of outcomes meant that for some outcomes (i.e., very good partial response [VGPR] and minimal residual disease [MRD] negativity) no inferences could be drawn about the numerical differences observed between the groups. OS data were not compared at the interim analysis but will be analyzed at the final analysis, which is expected in 2023.
- In their input to CADTH, clinicians indicated that a positive response to treatment includes maintenance or improvement in HRQoL. Patients emphasized the importance of this outcome when considering a new treatment. A formal comparison of HRQoL outcomes between treatment groups was not conducted in the IKEMA trial. Interpretation of the HRQoL data was further complicated by longer treatment exposure in the IsaKd group and the large number of patient withdrawals that occurred over time in the study. Patients in the IsaKd group showed little change from baseline in HRQoL scores over time, suggesting patients' quality of life was maintained; however, due to the limitations of the evidence, pERC was unable to draw definitive conclusions on the effect of IsaKd on patients' quality of life. Patients also identified reduced hospital visits as an important unmet need;

however, it was noted by clinicians that because IsaKd administration is associated with multiple visits to chemotherapy suites, this may not be feasible for some patients.

- pERC noted that in general, the incidence of AEs and serious adverse events (SAEs) was similar between the treatment groups in the IKEMA trial, although there were increases of infusion reactions and infections, particularly pneumonia, in the IsaKd group. Compared to the Kd group, the incidence of grade 3 or higher AEs was higher in patients treated with IsaKd, but this did not result in more treatment discontinuations. Despite an increase in some AEs, pERC considered the safety profile of IsaKd to be manageable.
- The drug plan and clinician input to CADTH indicated that Kd, the comparator in the IKEMA trial, is most often used in Canada as a third-line treatment option. Relevant comparators in the second-line setting include lenalidomide and dexamethasone, carfilzomib plus lenalidomide and dexamethasone (KRd), daratumumab plus lenalidomide and dexamethasone (DRd), and daratumumab plus bortezomib and dexamethasone (DVd). In the absence of direct evidence comparing IsaKd to these regimens (and others), the sponsor submitted 5 indirect treatment comparisons (1 network meta-analysis [NMA] and 4 matching-adjusted indirect comparisons [MAICs]) to estimate relative efficacy. pERC discussed that limitations related to heterogeneity introduced uncertainty into the results, particularly the unanchored MAICs. Consequently, pERC could not draw conclusions on the relative efficacy of IsaKd to other relevant comparators. There was no indirect evidence submitted to inform on the HRQoL or safety of IsaKd versus other relevant comparators.

Background

Isatuximab is administered as an IV infusion, at a dose of 10 mg/kg in combination with Kd and has a Health Canada indication for the treatment of adult patients with relapsed or refractory MM who have received 1 to 3 prior lines of therapy. Isatuximab is a mAb that binds to a specific extracellular epitope of CD38, triggering mechanisms that result in the death of CD38-expressing tumour cells. CD38 is a transmembrane glycoprotein with ectoenzymatic activity that is expressed in hematologic malignancies as well as other cell types and tissues. Each treatment cycle of IsaKd is 28 days; in cycle 1, isatuximab is administered on days 1, 8, 15, and 22 (weekly), and in cycle 2 and beyond it is administered every 2 weeks. Treatment is continued until disease progression or unacceptable toxicity.

Sources of Information Used by the Committee

To make their recommendation, pERC considered the following information:

- a review of 1 ongoing, phase III, open-label, randomized controlled trial in patients with relapsed or refractory MM
- patients' perspectives gathered by 1 patient group, Myeloma Canada
- input from public drug plans and cancer agencies that participate in the CADTH review process
- two clinical specialists with expertise diagnosing and treating patients with MM

- input from 2 clinician groups, including the Canadian Myeloma Research Group and the Ontario Health Cancer Care Ontario Hematology Cancer Drug Advisory Committee
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

Myeloma Canada submitted the patient input for this CADTH review. Myeloma Canada, founded in 2005, is the only national charitable organization created by and for Canadians impacted by MM. The organization is driven to improve the lives of those affected by myeloma. Information from this input was gathered through a patient survey. The survey was accessed through email and social media from April 22, 2021, to May 9, 2021. A total of 208 individuals with myeloma responded to the survey.

Most patients surveyed indicated that having access to an effective treatment was very important, as was controlling symptoms such as infections, kidney problems, mobility, neuropathy, and fatigue. Patients described impacts on their abilities to perform day-to-day activities such as working, travel, and exercise. Patients are seeking new and effective treatment options that would improve their quality of life, have maximum benefits with non-debilitating side effects, reduce their hospital visits, and help them achieve the longest remission possible in lieu of a cure. The patient group highlighted the importance of receiving information about emerging treatments and having timely access to these treatments.

Clinician Input

Input From the Clinical Experts Consulted by CADTH

According to the clinical experts consulted by CADTH, newer treatments are needed for MM that exhibit better disease control and less toxicity. In particular, needs are not being met for patients who are refractory to certain drug classes, like immunomodulators (lenalidomide) or proteasome inhibitors (bortezomib), and outcomes tend to be poor in these patients.

Isatuximab should be combined with other drugs that have unrelated mechanisms and toxicity profiles that can be used in any line of therapy. For patients with 1 prior line of therapy, an isatuximab regimen could be particularly useful if they had not received a prior anti-CD38 mAb. Whether there would be benefit for those previously treated with an anti-CD38 mAb is unknown.

There is no established method for determining which patients would most and least benefit from treatment. A clinically significant response would be improved PFS with acceptable toxicity and quality of life. Response should be assessed before each treatment cycle, and disease progression or unacceptable toxicity would warrant discontinuation of treatment.

Clinician Group Input

Input was submitted by the Canadian Myeloma Research Group and the Ontario Health Cancer Care Ontario Hematology Cancer Drug Advisory Committee. There were no notable differences between the input provided by the clinical experts consulted by CADTH on this review and the clinician groups. The clinician groups did not specifically comment on their

own experiences with IsaKd; however, they did note that they believed IsaKd would be useful in patients who relapsed who had progressed on lenalidomide and/or bortezomib.

Drug Program Input

The drug programs identified jurisdictional implementation issues related to considerations for initiating and prescribing of therapy, generalizability, a funding algorithm, care provision issues, and system and economic issues. pERC weighed evidence from the IKEMA trial and other clinical considerations, including input from the clinical experts consulted by CADTH, to provide responses to the drug plans' implementation questions, which are presented in Table 3.

Table 3: Responses to Questions From the Drug Programs

Implementation Issues	Response
Considerations for initiation of therapy	
The trial included patients who had 1 to 3 prior lines of treatment. Should eligibility for isatuximab align with that of the trial?	pERC agreed with the clinical experts that although the IKEMA trial excluded patients with > 3 prior lines of therapy, there is no reason that otherwise eligible patients should not have access to IsaKd assuming they have had no prior exposure to an anti-CD38 mAb. pERC agreed that this is an important consideration as new therapies come into the MM treatment space, and IsaKd may move further down the lines of therapy.
Do patients with high-risk cytogenetics exhibit a distinct response to IsaKd and should they be treated differently?	pERC agreed with the clinical experts that patients with high-risk cytogenetics do not have a distinct response to IsaKd and therefore should not be treated differently.
Considerations for renewal of therapy	
There is increasing interest in weekly carfilzomib dosing. Can the IKEMA trial data be generalized to use isatuximab with weekly Kd?	The clinical experts noted that weekly dosing of carfilzomib is already happening for some patients, and there is some evidence to support this approach. pERC agreed that weekly dosing has the potential to benefit patients and the health care system, as less of the drug and less chair time would be needed. pERC agreed that a weekly dosing schedule of carfilzomib could be considered with the IsaKd regimen.
If a component of the regimen has to be discontinued (e.g., carfilzomib or dexamethasone), should the regimen be discontinued altogether?	pERC agreed that if a component of the IsaKd regimen must be discontinued, there is no reason to discontinue the remaining components of the regimen as this was permitted in the IKEMA trial.
Generalizability	
Should the following patients be eligible for IsaKd: <ul style="list-style-type: none"> • those with ECOG Performance Status of 2 or greater • those with primary refractory MM • those with serum-free light chain measurable disease only • those with known amyloidosis? 	<p>The IKEMA trial enrolled patients with an ECOG Performance Status of ≤ 2. pERC recognized that Performance Status may be related to underlying disease; therefore, for some patients, an improvement in status is expected after initiation of treatment. As such, IsaKd could be considered in patients with an ECOG Performance Status > 2, and this decision should be left to the judgment of the treating clinician.</p> <p>The IKEMA trial excluded patients with primary refractory MM, serum-free light chain measurable disease only, and known amyloidosis concomitant with MM. pERC agreed with the clinical experts that these patients are likely to benefit from treatment with IsaKd and therefore should also be eligible for treatment.</p>

Implementation Issues	Response
<p>On a time-limited basis, should patients currently on Kd but whose disease has not yet progressed, be allowed to add isatuximab to their regimen?</p>	<p>pERC agreed with the clinical experts that patients currently receiving Kd whose disease has not progressed should be allowed to have isatuximab added to their regimen provided all other eligibility criteria are met.</p>
Funding algorithm (oncology only)	
<p>Which drugs may be preferred in what settings (or line of therapy): second-line DRd or DVd vs. second-line IsaKd; second-line IsaKd vs. third-line IsaPd?</p> <ul style="list-style-type: none"> • What evidence is available to support sequencing of isatuximab and daratumumab? • What evidence is available to support sequencing of IsaKd vs. IsaPd? 	<p>Second-line DRd or DVd vs. second-line IsaKd?</p> <ul style="list-style-type: none"> • pERC agreed with the clinical experts that the preferred regimen depends on what the patient has received previously. If a patient experienced disease progression on a lenalidomide-based regimen in the first-line setting, then IsaKd and DVd are available options. <p>Second-line IsaKd vs. third-line IsaPd?</p> <ul style="list-style-type: none"> • pERC agreed with the clinical experts that it is preferential to give an anti-CD38 as soon as possible; therefore, second-line IsaKd is preferred over third-line IsaPd for those who have not had a CD38 mAb. <p>What evidence is available to support sequencing of isatuximab and daratumumab?</p> <ul style="list-style-type: none"> • pERC agreed with the clinical experts that there is currently no evidence to support sequencing of isatuximab and daratumumab. <p>What evidence is available to support sequencing of IsaKd vs. IsaPd?</p> <ul style="list-style-type: none"> • pERC agreed with the clinical experts that there is currently no evidence in support of sequencing IsaKd and IsaPd.
<p>Isatuximab is administered as a prolonged IV infusion, per the product monograph. There is an ongoing clinical trial and there may be emerging data to administer a rapid infusion over 30 minutes if previous doses were tolerated. Can isatuximab be administered as a rapid infusion to minimize resource utilization and increase patient convenience?</p>	<p>In the absence of safety data on isatuximab administered as a rapid infusion, pERC agreed that this approach should not be used for administering IsaKd.</p>
Care provision issues	
<p>Additional comments:</p> <ul style="list-style-type: none"> • Isatuximab is available as 100 mg/5 mL and 500 mg/25 mL vials. Unused portions of a vial must be discarded, making vial sharing difficult. • The combination of carfilzomib and isatuximab would increase workload for pharmacy staff to prepare vs. other comparators. Carfilzomib vials require time and care for reconstitution. Weekly dosing schedules of carfilzomib may reduce the workload intensity for pharmacy staff. 	<p>pERC acknowledged the care provision issues identified by the drug plans.</p>

Implementation Issues	Response
System and economic issues	
<p>Additional comments (response not required):</p> <ul style="list-style-type: none"> • Concerns regarding the anticipated budget impact and sustainability <ul style="list-style-type: none"> ◦ In the New Drug Scenario, the cost of isatuximab was estimated to be \$11,363,785; \$22,893,854; and \$43,663,841 in years 1, 2, and 3, respectively. The corresponding budget impact for IsaKd was calculated to be \$12,912,347 in year 1; \$31,121,521 in year 2; and \$54,944,905 in year 3. • Presence of confidential negotiated prices for comparators <p>There are confidential prices for carfilzomib as part of the Kd and KRd regimens.</p>	<p>pERC acknowledged the substantial budget impact associated with IsaKd and noted this must be improved as a reimbursement condition as well as substantial price reductions to improve cost-effectiveness.</p> <p>pERC also acknowledged that, given the magnitude of the price reductions required, it is unlikely any negotiated prices will change the conclusions.</p>

DRd = daratumumab plus lenalidomide and dexamethasone; DVd = daratumumab plus bortezomib and dexamethasone; ECOG = Eastern Cooperative Oncology Group; IsaKd = isatuximab plus carfilzomib and dexamethasone; IsaPd = isatuximab plus pomalidomide and dexamethasone; KRd = carfilzomib plus lenalidomide and dexamethasone; Kd = carfilzomib and dexamethasone; mAb = monoclonal antibody; MM = multiple myeloma; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; vs. = versus.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

The CADTH systematic review included 4 reports of 1 pivotal trial (IKEMA). No additional studies were identified from the literature. IKEMA is an ongoing, sponsor-funded, multinational (with Canadian sites), open-label, randomized controlled trial that randomized 302 adult (> 18 years) patients with relapsed and/or refractory MM and 1 to 3 prior lines of therapy, in a 3:2 manner, to either IsaKd or Kd. Patients in the IsaKd group received isatuximab 10 mg/kg by IV infusion in 28-day cycles (weekly during the first cycle, then every 2 weeks for the subsequent cycles) with carfilzomib 20 mg/m² on days 1 and 2, then escalated to 56 mg/m² IV for days 8, 9, 15 and 16 of cycle 1 and days 1, 2, 8, 9, 15 and 16 for the subsequent cycles, and dexamethasone 20 mg twice weekly. Patients in the Kd group received carfilzomib and dexamethasone at those same dose regimens. Patients were treated until they experienced disease progression, unacceptable toxicity, or the patient decided to discontinue study treatment. Randomization was stratified by the number of prior lines of therapy (1 versus > 1) and the Revised International Staging System score (I or II versus III versus not classified).

The primary outcome of the IKEMA trial was PFS, and the key secondary outcomes included ORR, VGPR or better rate, duration of response (DOR), time to first response (TTR), MRD negativity in patients with VGPR or better, as well as complete response (CR) rate, and OS. PFS, ORR, VGPR or better, and MRD negativity in patients with VGPR or better were included in the statistical testing hierarchy. HRQoL was assessed as an exploratory outcome. The findings in this report are from an interim analysis, which was preplanned to take place once 103 disease progression events had occurred (information fraction of 65%). Results for the

final analysis, including OS data, are not expected until 2023. Harms, including AEs, SAEs, and AEs of special interest, were also measured and reported.

Patients were an average of 63.1 years of age (standard deviation [SD] = 9.9), 56% were male and 70.9% were White. The majority of patients were of the immunoglobulin G subtype (67.9%) at diagnosis, followed by immunoglobulin A (22.8%), and these percentages were similar to those observed at study entry (69.9% and 22.5%, respectively). The most common International Staging System stage at study entry was stage I (53.0%), followed by stage II (31.1%) and stage III (15.2%). The majority of patients were relapsed and refractory (71.5%), while the remainder were relapsed (28.5%). The average number of prior regimens was 3.2 (SD = 1.7) and the number of prior lines was 1.8 (SD = 0.8). Patients were most commonly refractory to an iMiD (45.0% of patients) followed by a PI (33.1%), or both (20.5%).

Efficacy Results

PFS was the primary outcome of the IKEMA trial, and at the interim analysis (median follow-up of 20.73 months), median PFS was not reached in the IsaKd group and was 19.15 months (95% CI, 15.77 to not calculable) in the Kd group, for a stratified HR of 0.531 (99% CI, 0.318 to 0.889), and a P value, according to a stratified log rank test, of $P = 0.0007$. In the IsaKd group, 26.8% of patients had a PFS event, while in the Kd group, 44.7% of patients had a PFS event. The results for sensitivity analyses performed for the primary outcome were consistent with the primary analysis, and preplanned subgroup analyses revealed consistent results across various subgroups of interest for this review.

OS will be assessed at the end of the study; therefore, no median OS data were available at the time of the interim analysis.

HRQoL was assessed using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Cancer Specific Questionnaire with 30 items, the EORTC Quality of Life MM Specific Module with 20 items, and the EQ-5D 5-Levels instruments. Interpretation of HRQoL data were limited by the large number of withdrawals over time in the study; however, generally, for the EORTC instruments, there was little change from baseline in HRQoL scores in the IsaKd group and numerical increases from baseline over time were observed in the Kd group. An increase in score on these instruments indicates an improvement in HRQoL.

The ORR was assessed in all responders (patients achieving either a stringent complete response [sCR], CR, VGPR, or partial response) and in patients achieving a VGPR or better. An sCR was defined as patients having a CR with a normalized serum-free light chain ratio in the absence of bone marrow plasma cells when assessed by immunohistochemistry or immunofluorescence. The percentage of patients responding was 86.6% in the IsaKd group and 82.9% in the Kd group, and the between-group difference was not statistically significant ($P = 0.1930$). Because this was the second outcome in the statistical hierarchy, testing was to have halted for subsequent outcomes, although the sponsor continued to conduct testing and report P values for descriptive purposes. The percentage of patients achieving a VGPR or better was 72.6% in the IsaKd group and 56.1% in the Kd group. No patients achieved an sCR, while 39.7% of patients in the IsaKd group and 27.6% of patients in the Kd group achieved a CR, and 33.0% and 28.5% of patients, respectively, achieved a VGPR. MRD negativity was achieved by 29.6% of patients in the IsaKd group and 13.0% of patients in the Kd group.

The median DOR was calculated based on 155 patients in the IsaKd group and 102 patients in the Kd group. The median DOR was not yet reached in either treatment group and the HR

was 0.425 (95% CI, 0.269 to 0.672). The median time to first response was 1.08 months (95% CI, 1.05 to 1.12) in the IsaKd group and 1.12 months (95% CI, 1.05 to 1.18) in the Kd group, for a stratified HR of 1.143 (95% CI, 0.888 to 1.471).

Harms Results

There were 97.2% of patients in the IsaKd group and 95.9% of patients in the Kd group who had at least 1 AE; 76.8% versus 67.2%, respectively, who had at least a grade 3 AE or greater; and 3.4% versus 3.3% who had a grade 5 AE. The most common AE in the IsaKd group was infusion-related reaction, which occurred in 44.6% of patients in the IsaKd group and 3.3% of patients in the Kd group. Other common AEs (IsaKd versus Kd) included hypertension (36.7% versus 31.1%), diarrhea (36.2% versus 28.7%), upper respiratory tract infection (36.2% versus 23.8%), fatigue (28.2% versus 18.9%), and dyspnea (27.7% versus 21.3%). The most common grade 3 or greater AEs (IsaKd versus Kd) were hypertension (20.3% versus 19.7%) and pneumonia (16.4% versus 12.3%).

SAEs occurred in 59.3% of patients in the IsaKd group and 57.4% of patients in the Kd group. The most common SAE was pneumonia (18.1% in the IsaKd group versus 11.5% in the Kd group).

There were 8.5% of patients in the IsaKd group and 13.9% of patients in the Kd group who had an AE leading to definitive treatment discontinuation. There was 1 patient who discontinued treatment of isatuximab due to an AE.

Among notable harms, respiratory tract infections occurred in 83.1% of patients in the IsaKd group and 73.8% of patients in the Kd group, and these were grade 3 or greater events in 32.2% versus 23.8% of patients, respectively. Cardiac disorders occurred in 7.3% of patients treated with IsaKd versus 5.7% of patients treated with Kd. Second primary malignancies (i.e., solid, non-skin) occurred in 2.8% versus 3.3% of patients in the IsaKd and Kd groups, respectively, and second primary malignancies (i.e., solid, skin) in 5.1% versus 2.5% of patients, respectively. There were no hematologic malignancies reported. Events of decreased neutrophil counts occurred in 54.8% of patients in the IsaKd group versus 43.4% of patients in the Kd group, and grade 3 or greater events occurred in 19.2% versus 7.4% of patients, respectively. Events of decreased platelet counts occurred in 94.4% of patients treated with IsaKd and 87.7% of patients treated with Kd, and these were grade 3 or greater events in 29.9% versus 23.8% of patients, respectively.

Critical Appraisal

IKEMA was an open-label trial and lack of blinding may have biased results, particularly for patient-reported outcomes such as HRQoL and reporting of harms. Assessment of response was conducted by a blinded independent review committee and therefore is unlikely to have been influenced by lack of blinding.

The results of the IKEMA trial were based on a preplanned interim analysis, with an information fraction of 65%; therefore, there is a risk of over-estimation of the primary effect for PFS. However, given the statistically and clinically significant difference observed between the groups for PFS, the potential for over-estimation is unlikely to have altered the conclusions.

Multiplicity was controlled for with the use of a hierarchical testing procedure; however, early failure of the hierarchy meant that statistical testing was only conducted on the primary and

modifier that reflects differences in care over the wide time span during which the trials were conducted. Previous lenalidomide use was specifically noted as a likely effect modifier by 1 of the clinical experts, and prior treatment in general. As for the choice of the matching factors, it was based on internal expert opinion (rather than a survey of clinical experts) and availability and completeness of data in the trials (which is inconsistent with the National Institute for Health and Care Excellence’s Decision Support Unit guidelines that recommend the identification of key factors in the data).

The reported effective sample sizes and the skewness and outliers apparent in the visualizations of the weight distributions suggest the results may be heavily influenced by a small subset of patients from the IKEMA trial. Generalizability may also be an issue due to the small sample size remaining after exclusions and matching, as the remaining patients and weighted sample are unlikely to be representative of the entire patient population.

Economic Evidence

Table 4: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model
Target population	Adults with relapsed or refractory multiple myeloma who have received 1 to 3 lines of prior therapy
Treatment	IsaKd
Submitted price	Isatuximab, 6 mL (100 mg/5 mL), IV injection: \$757.90 Isatuximab, 30 mL (500 mg/25 mL), IV injection: \$3,789.49
Treatment cost	The sponsor’s calculated cost (including administration costs, relative dose intensity, and wastage) of IsaKd is \$36,569 for the first 28-day cycle and \$29,023 for subsequent cycles.
Comparator	Kd
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (37 years)
Key data source	IKEMA randomized controlled trial

Component	Description
<p>Key limitations</p>	<ul style="list-style-type: none"> • The sponsor assumed that median survival for IsaKd would be 10 years, and that after 30 years, when patients would be older than 90 years, 10% of the cohort would remain alive. These assumptions resulted in substantial survival (life-year) gains with IsaKd relative to Kd. An OS benefit with IsaKd has not been shown in clinical trials, and OS data from the IKEMA trial is immature. Assuming an OS benefit in the absence of evidence is challenging due to the potential impact of subsequent therapy. The potential impact of subsequent treatment after disease progression was not considered in the sponsor's model. Clinical experts consulted by CADTH indicated that the OS predicted by the sponsor's model for IsaKd was not likely clinically plausible based on Canadian data. • Relevant treatment comparators (e.g., DVd) were not included in the sponsor's base case. The comparative effectiveness of IsaKd to relevant comparators is highly uncertain, owing to a lack of head-to-head trials and limitations with the sponsor's indirect treatment comparisons. • The model lacked flexibility to assess cost-effectiveness by line of therapy (e.g., second-line, third-line, or later) or type of prior treatment received, and in relevant subgroups (e.g., patients who are transplant eligible or ineligible). Given that there is considerable heterogeneity across these subgroups in terms of comparators and prognosis, this increases the uncertainty of the analysis. • The extrapolation of time to treatment discontinuation lacked face validity in that the sponsor's model predicted that patients who received IsaKd would remain disease free for several years following discontinuation of all treatments, which is unlikely according to clinical experts. • The sponsor assumed that among patients in the progression-free state, those on active treatment were assumed to have higher quality of life than those who had discontinued treatment but not progressed. This assumption is problematic as assessing utilities at time of discontinuation may capture AEs that are acute not chronic. The impact of different types of disease progression (e.g., serological, clinical) and the impact of subsequent treatment on quality of life was not considered in the sponsor's model (i.e., those who receive subsequent treatment may have a differing utility value compared to those who do not receive subsequent treatment). • RDI was used to reduce drug costs; however, this assumes a direct link between RDI and drug cost, which may not hold. For example, a delayed dosing schedule may reduce RDI but not overall costs if the patient eventually makes it back to the recommended dosing schedule post trial. Likewise, it is unclear with RDI if this interacts with treatment discontinuation, which may double count the cost reduction due to a missed dose. • The impact of AEs on the ICER is highly uncertain, given that only costs related to grade 3 or higher AEs that affected at least 5% of IKEMA participants were included in the model, which may underestimate the impact of rare AEs and does not capture all AEs noted to be important to clinicians. Further, the assumption that each AE could occur only once during the 37-year analysis horizon lacks face validity. Quality of life effects were assumed to be captured as part of health state utility values, which is unlikely and may not account for differences in AEs between treatments. • The sponsor assumed that all patients would receive subsequent treatment after disease progression, which is unlikely based on clinical expert feedback. Subsequent treatments were assumed to affect costs only, and the impact of subsequent treatment on OS was not considered.

Component	Description
CADTH reanalysis results	<ul style="list-style-type: none"> Given the limitations associated with the chosen modelling approach and the lack of informative comparative data for most relevant comparators, the cost-effectiveness of IsaKd is highly uncertain. CADTH undertook an exploratory reanalysis to correct the sponsor’s model using best available evidence, but the validity and interpretability of the results are impacted by the previously noted limitations. Given the limitations, CADTH was unable to correct for items such as the exclusion of lower cost comparators, unclear model coding, and assumed proportional hazards. As such, the CADTH exploratory reanalysis likely underestimates the true ICER of IsaKd. CADTH’s exploratory reanalyses included correcting the price of bortezomib, adopting alternative parametric distributions for OS, using the IKEMA PFS hazard ratio to model the relationship between IsaKd and Kd, assuming correlation between PFS and TTD, revising the utility values for PFS, including disutility values, and assuming that all patients receive the full dose of all drugs. CADTH was unable to address the limitations with the chosen modelling approach, the lack of head-to-head comparative clinical data for additional relevant comparators, the cost-effectiveness of IsaKd in relevant subgroups, and uncertainty associated with subsequent therapy after disease progression. Compared with Kd, the ICER for IsaKd was \$1,588,632 per QALY, which is highly sensitive to the extrapolation of immature OS data from the IKEMA trial. The results of these reanalyses should be viewed only as exploratory given the previously noted limitations. IsaKd would not be considered cost-effective at a \$50,000 per QALY willingness-to-pay threshold with a 100% price reduction to isatuximab, due to the high cost of carfilzomib. For IsaKd to be considered cost-effective at a \$50,000 per QALY willingness-to-pay threshold, a 100% price reduction of isatuximab and a 61% price reduction of carfilzomib would be required.

AEs = adverse events; DVd = daratumumab plus bortezomib and dexamethasone; ICER = incremental cost-effectiveness ratio; IsaKd = isatuximab plus carfilzomib and dexamethasone; Kd = carfilzomib and dexamethasone; LY = life-year; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life-year; RDI = relative dose intensity; TTD = time to treatment discontinuation.

Budget Impact

CADTH identified the following key limitations with the sponsor’s analysis: the number of patients eligible for IsaKd is uncertain; not all relevant comparators were included; the market uptake of IsaKd is uncertain; relative dose intensity was inappropriately used to reduce drug costs; the duration of treatment is uncertain; and there was misalignment between the sponsor’s submitted pharmacoeconomic model and the budget impact analysis for some parameters. The CADTH reanalyses included assuming a relative dose intensity of 100% for all drugs and aligning inputs with the pharmacoeconomic model where possible.

Based on the CADTH reanalyses, the budget impact of introducing IsaKd for the treatment of relapsed or refractory MM is expected to be \$15,780,928 in year 1; \$36,288,445 in year 2; and \$65,035,119 in year 3, with a 3-year total budget impact of \$117,104,492. The estimated budget impact is sensitive to the prevalence of MM, the market uptake of IsaKd, and the duration of treatment.

pERC Information

Members of the Committee

Dr. Maureen Trudeau (Chair), Dr. Catherine Moltzan, Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Matthew Cheung; Dr. Winson Cheung, Dr. Michael Crump, Dr. Leela John, Dr. Christian

Kollmannsberger, Mr. Cameron Lane, Dr. Christopher Longo, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

Meeting date: December 1, 2021

Regrets: None

Conflicts of interest: None