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Reimbursement Recommendation

Ciltacabtagene Autoleucel (Carvykti)

Indication: For the treatment of adult patients with multiple myeloma, who have received 1 to 3 prior lines of therapy, including a proteasome inhibitor and an immunomodulatory agent, and who are refractory to lenalidomide.

Sponsor: Janssen Inc.

Final Recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Carvykti?

Canada's Drug Agency (CDA-AMC) recommends that Carvykti should be reimbursed by public drug plans for the treatment of adult patients with multiple myeloma (MM), who have received 1 to 3 prior lines of therapy, including a proteasome inhibitor and an immunomodulatory drug, and whose disease is refractory to lenalidomide if certain conditions are met.

Which Patients Are Eligible for Coverage?

Carvykti should only be covered to treat patients aged 18 years or older with documented diagnosis of MM, who have received 1 to 3 prior lines of therapy, and have a good performance status, as determined by a specialist. Carvykti should not be reimbursed for the treatment of patients whose MM is affecting their central nervous system. It should also not be reimbursed for patients who have previously received any treatment that targets B-cell maturation antigen (BCMA).

What Are the Conditions for Reimbursement?

Carvykti should only be reimbursed if it is prescribed and administered by clinicians with expertise in the treatment of MM at specialized centres with adequate infrastructure, resources, and expertise to facilitate treatment with chimeric antigen receptor (CAR) T-cell therapy, and the cost of Carvykti is reduced.

Why Did CDA-AMC Make This Recommendation?

- Evidence from a clinical trial demonstrated that Carvykti prolonged the time until disease progression or death and was associated with an improved response to treatment.
- Based on our assessment of the health economic evidence, Carvykti does not represent good value to the health care system at the public list price. A price reduction is therefore required.
- Carvykti met some patient needs because it is a one-time treatment that offers an alternative option, delays disease progression, and may help reduce MM symptoms without worsening the patient's overall quality of life.
- The implementation of Carvykti, including in earlier lines of therapy, may raise several ethical and equity considerations related to access and resource allocation because of the resource-intensive nature of CAR T-cell therapy and the currently limited number of CAR T-cell centres in Canada.

Summary

- Based on public list prices, Carvykti is estimated to cost public drug plans approximately $477 million over the next 3 years.

Additional Information

What Is MM?

MM is a cancer of plasma cells (the white blood cells that make immunoglobulins) in the bone marrow. In 2023, approximately 3,900 people in Canada were diagnosed with MM.

Unmet Needs in MM

MM is a disease with poor prognosis and many patients do not respond to initial treatments and their disease will relapse. This prognosis leaves patients trying many different treatments. There is a need for additional effective treatment options that can delay disease progression, prolong survival, reduce side effects, and improve the quality of life for both patients and their caregivers.

How Much Does Carvykti Cost?

Treatment with Carvykti is associated with a one-time infusion cost of $632,455.

Recommendation

The pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommends that ciltacabtagene autoleucel (cilta-cel) be reimbursed for the treatment of adult patients with MM, who have received 1 to 3 prior lines of therapy, including a proteasome inhibitor and an immunomodulatory drug, and whose disease is refractory to lenalidomide, only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One ongoing phase III, open-label, randomized, multicentre study (CARTITUDE-4; N = 419) demonstrated that treatment with cilta-cel results in added clinical benefit for patients with MM, who have received 1 to 3 prior lines of therapy, including a proteasome inhibitor and an immunomodulatory drug, and whose disease is refractory to lenalidomide, when compared with a physician's choice of standard of care (SOC) therapies of either pomalidomide-bortezomib-dexamethasone or daratumumab-pomalidomide-dexamethasone. The CARTITUDE-4 trial demonstrated that treatment with cilta-cel, compared to SOC, was associated with statistically significant and clinically meaningful improvements in progression-free survival (PFS) in patients whose MM relapsed or is refractory (hazard ratio [HR] = 0.26; 95% confidence interval [CI], 0.18 to 0.38). Results for complete response (CR) or better rate (73.1% versus 21.8% for cilta-cel versus SOC; odds ratio [OR] = 10.3; 95% CI, 6.5 to 16.4) and minimal residual disease (MRD) negativity rate (60.6% versus 15.6% for cilta-cel versus SOC; OR = 8.7; 95% CI, 5.4 to 13.9) were supportive of PFS findings.

Patients identified the need for more effective and accessible treatment options that prolong survival, minimize side effects, and improve quality of life for patients and caregivers. pERC noted that treatment with cilta-cel met some of the needs identified by patients because it is a one-time therapy that provides an additional treatment option with improved PFS and may result in improvement in MM-related symptoms without deterioration in health-related quality of life (HRQoL). The committee discussed that the safety profile of cilta-cel was consistent with the known safety profile of the treatment with likely no difference in serious adverse events (AEs) across the study groups.

Using the sponsor-submitted price for cilta-cel and publicly listed prices for all other drugs, the incremental cost-effectiveness ratio (ICER) for cilta-cel was $280,871 per quality-adjusted life-year (QALY) gained compared with bortezomib and dexamethasone. At this ICER, cilta-cel is not cost-effective at a willingness-to-pay threshold of $50,000 per QALY gained for adult patients with MM, who have received 1 to 3 prior lines of therapy, including a proteasome inhibitor and an immunomodulatory drug, and whose disease is refractory to lenalidomide. A price reduction is required for cilta-cel to be considered cost-effective at a threshold of $50,000 per QALY gained. In the absence of long-term data, uncertainties in the comparative evidence versus relevant comparators, immaturity of overall survival (OS) data, and limitations in how the submitted analysis models subsequent therapies, the cost-effectiveness of cilta-cel is highly uncertain.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Cilta-cel should be reimbursed in adult patients aged 18 years or older who meet all of the following criteria: 1.1. documented diagnosis of MM 1.2. have received 1 to 3 prior lines of therapy, including a proteasome inhibitor and an immunomodulatory drug 1.3. refractory to lenalidomide 1.4. have good performance status.	In the CARTITUDE-4 trial, treatment with cilta-cel demonstrated a clinical benefit in adult patients with a documented diagnosis of MM who met the characteristics listed in the condition.	pERC agreed with the clinical experts that patients with an ECOG Performance Status of more than 1 may be treated at the discretion of the treating physician.
2. Cilta-cel should not be initiated in patients with active CNS involvement or exhibiting signs of meningeal involvement of MM.	The CARTITUDE-4 trial excluded patients with known active or prior history of CNS involvement or exhibiting clinical signs of meningeal involvement of MM. There was no evidence from the trial regarding the potential benefit and harm of cilta-cel therapy in these patients.	pERC noted it would be appropriate to consider patients with controlled CNS metastases for eligibility.
3. Cilta-cel should not be reimbursed in patients who have received prior treatment with any therapy that is targeted to BCMA, or prior anti-BCMA CAR T-cell therapy.	Patients with prior exposure to CAR T-cell therapy or any therapy that is targeted to BCMA were not included in the CARTITUDE-4 trial; therefore, the efficacy and safety of cilta-cel following either of these therapies is unknown.	—
Prescribing		
4. Treatment with cilta-cel is a one-time therapy.	The CARTITUDE-4 trial did not evaluate the efficacy and safety of cilta-cel in a repeat therapy setting and there is no supporting evidence regarding the use of cilta-cel beyond a one-time therapy.	—
5. Cilta-cel should only be prescribed by clinicians with expertise in the treatment of MM. Cilta-cel should be administered in specialized centres with adequate infrastructure, resources, and expertise to facilitate treatment with CAR T-cell therapy.	To ensure that cilta-cel is prescribed only for appropriate patients and adverse events are managed in an optimized and timely manner.	pERC acknowledges that the current limited availability of specialized centres with adequate infrastructure and resources to administer CAR T-cell therapy in Canada is a barrier that needs to be addressed.
Pricing		
6. A reduction in price.	The treatment landscape for MM is evolving. Based on our reanalysis, when comparing cilta-cel to currently used	—

Reimbursement condition	Reason	Implementation guidance
	treatments, a price reduction of more than 80% would be required to be cost-effective at a WTP threshold of $50,000 per QALY gained (88% if bortezomib and dexamethasone are considered relevant comparators). These price reductions are based on uncertain extrapolations of OS given the immaturity of OS data for those receiving cilta-cel and the lack of robust comparative evidence. Given the uncertainty surrounding long-term comparative efficacy and the impact on subsequent therapy costs, the required price reduction to achieve a given threshold is uncertain.	
Feasibility of adoption		
7. The economic feasibility of the adoption of cilta-cel must be addressed	At the submitted price, the incremental budget impact of cilta-cel is expected to be greater than $40 million in years 1, 2, and 3.	—
8. Organizational feasibility 8.1. The administration of cilta-cel requires expertise, infrastructure, and human resources to ensure that the treatment and adverse events are managed in an optimized and timely manner for patients. 8.2. Prioritization considerations may include patient prognosis, prior therapy, and/or geographic location if cilta-cel exceeds manufacturing or delivery capacity.	Due to the resource-intensive nature of CAR T-cell therapy and currently limited human resources and logistical constraints, a standardized process to prioritize use should be developed to promote treatment for the optimal clinical benefit in an ethical and equitable manner.	—

cilta-cel = ciltacabtagene autoleucel; BCMA = B-cell maturation antigen; CAR = chimeric antigen receptor; CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; MM = multiple myeloma; OS = overall survival; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; QALY = quality-adjusted life-year; WTP = willingness-to-pay.

Discussion Points

- pERC deliberated on the results of the phase III CARTITUDE-4 trial and noted that although the risk difference in PFS at 24 months was not available, the observed trend of differences at 24 months was consistent with that at 12 months and treatment with cilta-cel was likely to result in a clinically meaningful increase in the probability of being alive and progression-free at 24 months compared to SOC. Available efficacy results were assessed at having high certainty as per the Grading of

Recommendations, Assessment, Development, and Evaluations (GRADE) assessment of the evidence. pERC observed that treatment with cilta-cel resulted in statistically significantly better response rates than SOC, as demonstrated by significantly better improvements in CR or better rate, very good partial response (VGPR) or better rate, and overall response rate (ORR) in the cilta-cel group compared with the SOC group. The committee noted that the GRADE assessment indicated a high certainty in the evidence and acknowledged that this is a clinically meaningful benefit of treatment with cilta-cel.

- pERC acknowledged the importance of OS to patients with cancer. However, the committee noted that the OS data were immature, and the OS analysis conducted at a later data cut-off of December 13, 2023, was not controlled for the overall type I error; therefore, the results were considered as descriptive supportive evidence only.
- In the absence of a direct comparison of cilta-cel and other relevant treatment options for the indication of interest, pERC considered evidence from 2 sponsor-submitted indirect treatment comparison (ITC) reports: 1 involving 4 comparators (i.e., carfilzomib-dexamethasone, bortezomib-dexamethasone, daratumumab-bortezomib-dexamethasone, and pomalidomide-dexamethasone) and the other involving 2 comparators (i.e., isatuximab-pomalidomide-dexamethasone and selinexor-bortezomib-dexamethasone). Results of the sponsor-submitted ITCs suggested that cilta-cel demonstrated statistically significant improvements in terms of PFS (for all comparisons), and OS (for the comparisons versus pomalidomide-dexamethasone, bortezomib-dexamethasone, daratumumab-bortezomib-dexamethasone, and selinexor-bortezomib-dexamethasone), but no statistically significant differences were shown in terms of OS in the comparisons of cilta-cel versus carfilzomib-dexamethasone and isatuximab-pomalidomide-dexamethasone. However, pERC noted that the indirect evidence was associated with notable limitations including incomplete adjustment of important effect modifiers and concern of restricted generalizability to the clinical setting in Canada; therefore, a definite conclusion could not be provided regarding the clinical benefit of cilta-cel compared to the previously mentioned comparators.
- pERC noted that although cilta-cel is associated with significant short-term toxicity (e.g., infections, cytokine-release syndrome, and gastrointestinal disorders), it is a one-time therapy that provides a treatment-free interval for patients. However, pERC acknowledged that ongoing support is needed after receiving cilta-cel. pERC could not provide definitive conclusions about the safety of cilta-cel relative to other treatments currently available because neither direct nor indirect comparative evidence was available.
- pERC noted cilta-cel must be administered at specialized treatment centres with the infrastructure and resources required to administer the treatment and manage AEs. However, currently, a limited number of centres in Canada have the expertise and resources to deliver CAR T-cell therapy and it is unlikely that qualified centres will be available in all jurisdictions. pERC acknowledged that a standardized process to prioritize use should be developed if capacity constraints occur to deliver this treatment for the greatest clinical benefit in an ethical and equitable manner. pERC noted that it is not

the committee's mandate to decide the allocation of resources or prioritization of patients to receive treatment.

- pERC discussed ethical and equitable considerations in the treatment of relapsed or refractory MM (r/r MM), including uncertainties in the evidence for cilta-cel and resultant implications for consent conversations, the stewardship of limited health budgets, as well as the need for collection of long-term data on safety, efficacy, and comparative effectiveness, especially in earlier lines of therapy to better support decision-making within clinical and health systems. The committee acknowledged preliminary evidence indicating that CAR T-cell therapies may pose a class-level risk of secondary T-cell lymphomas. Although this was not observed in the CARTITUDE-4 trial, the committee recognized the importance of robust consent conversations to inform patients about this risk and the need for life-long monitoring.
- pERC discussed the need for fair and equitable priority-setting criteria if the demand for cilta-cel exceeds manufacturing or delivery capacity. The committee noted that clinicians may experience moral distress in the face of capacity constraints and the need for difficult prioritization decisions. The committee acknowledged that clinical experts noted that cilta-cel, as a potential one-time therapy, may improve equitable access to treatment for patients residing in rural or remote communities, given the expected reduction in need for frequent travel associated with accessing alternative treatments for MM. The need for adequate financial support to facilitate equitable access and mitigate cost-related barriers to access that are exacerbated by geography were also discussed.
- pERC noted that the cost-effectiveness of cilta-cel is contingent on long-term OS and the impact on current treatment pathways. Due to the absence of evidence and limitations with the submitted analysis neither aspect could be actively explored. The analysis predicts large improvements in OS (between 2.6 and 4.3 years) depending on the comparator. It is uncertain whether this degree of benefit will be realized without access to longer term data. As cilta-cel is a new treatment class in this space, its addition will shift the treatment pathway for MM. Clinical experts noted that cilta-cel may not displace other therapeutic options, but instead become an additional option for patients with MM. The impact of pathway shifts could not be actively explored in the submitted analysis making the assessment of cost-effectiveness highly uncertain.

Background

MM is a hematological malignancy characterized by clonal proliferation of malignant plasma cells (B-cells) driven by an oncologic event and consequent overproduction of the abnormal immunoglobulin monoclonal protein (M protein). The estimated number of newly diagnosed cases of MM was 4,000 in 2022 and 3,900 in 2023 in Canada. Based on the reported prevalence of MM in 2018 and the growing projected annual incidence rate combined with a predicted 5-year survival rate, the projected prevalence of MM is estimated to be approximately 17,568 in Canada (excluding Quebec) in 2025. Most patients will have disease that relapses and many patients will have disease that becomes refractory to commonly used therapies. Patients with r/r MM often undergo multiple rounds of treatment, with the duration of remission, depth of

response, PFS, and OS decreasing with each subsequent line of therapy. According to the clinical experts and clinician groups, the main treatment goals for patients with r/r MM are to prolong survival, improve symptoms, minimize toxicities, and improve HRQoL. Therapies for the treatment of patients with r/r MM, and the sequencing of these treatments, depends on eligibility for autologous stem cell transplant at diagnosis, age, comorbidities, previous treatments, prior toxicities, and line of therapy. Available treatment options for patients with r/r MM in Canada include triplet therapy consisting of proteasome inhibitors, immunomodulatory drugs, or monoclonal antibodies, and CAR T-cell therapy (i.e., cilta-cel, which is under consideration for negotiation at the pan-Canadian Pharmaceutical Alliance).

Cilta-cel has been approved by Health Canada for the treatment of adult patients with MM, who have received 1 to 3 prior lines of therapy, including a proteasome inhibitor and an immunomodulatory drug, and whose disease is refractory to lenalidomide. Cilta-cel is a CAR T-cell therapy and is available as cell suspension in an infusion bag and the dosage recommended in the product monograph is 0.5 to 1.0 × 10^6 CAR-positive viable T-cells per kilogram body weight with a maximum of 1 × 10^8 CAR-positive viable T-cells. We previously reviewed cilta-cel for the treatment of adult patients with r/r MM, who have received at least 3 prior lines of therapy, including a proteasome inhibitor, an immunomodulatory drug, and an anti-CD38 antibody, and whose disease is refractory to their last treatment.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 phase III, open-label, randomized, active-control randomized controlled trial (CARTITUDE-4) in patients with r/r MM; 2 ITC reports including inverse probability of treatment weighting (IPTW) analyses for 4 comparators and matching-adjusted indirect comparison (MAIC) analyses for 2 comparators
- patients' perspectives gathered by 1 patient group, Myeloma Canada
- input from public drug plans that participate in the CDA-AMC review process
- input from 2 clinical specialists with expertise diagnosing and treating patients with r/r MM
- input from 2 clinician groups, including the Ontario Health (OH)-Cancer Care Ontario (CCO) Hematology Cancer Drug Advisory Committee and Canadian Myeloma Research Group
- a review of the pharmacoeconomic model and report submitted by the sponsor
- a review of relevant ethical issues related to cilta-cel.

Perspectives of Patients, Clinicians, and Drug Programs

Patient Input

We received 1 patient group submission from Myeloma Canada. Myeloma Canada is a patient advocacy group to support patients diagnosed with MM living in Canada.

Myeloma Canada collected data from patients with r/r MM (or their caregivers) who received 1 to 3 prior lines of therapy and were refractory to lenalidomide or had experience with a CAR T-cell therapy through a survey across Canada and internationally, by email and social media from April 5 to April 24, 2024. There were 53 eligible respondents from Alberta (3), British Columbia (12), Newfoundland and Labrador (2), Ontario (29), Quebec (5), and 2 from outside of Canada, both from France. There were 2 subsets of survey respondents: 1 included 37 patients or caregivers who met the criteria for the indication under review, and the other had 16 respondents with CAR T-cell therapy experience, of which 8 patients or caregivers had experience with cilta-cel and 8 patients or caregivers had experience with a different CAR T-cell therapy.

In terms of MM disease complications, infections were the most important aspect to control followed by kidney issues. Patients and/or caregivers also reported that MM had various impacts on their quality of life such as the ability to travel and interruption of life goals or accomplishments. Regarding MM treatment options, most patients and caregivers identified a need for effective treatments, with manageable side effects, and minimal impact on quality of life. Among the 37 patients or caregivers who met the criteria of the indication under review, 22 respondents reported receiving 3 lines of therapy, and 2 respondents reported treatment with BCMA-targeted therapy. Conversely, the experiences shared from patients and/or caregivers who received CAR T-cell therapy were generally positive. Of the 8 respondents who received cilta-cel, 5 of them rate the treatment extremely effective and the side effects extremely tolerable. Cytokine-release syndrome (CRS) was perceived to be the most concerning side effect by patients who met the criteria for the indication under review; however, it was considered tolerable for respondents who had received cilta-cel. There were 28 respondents out of 37 who found that an estimated minimum 1.25 years of extended life without needing active treatment to control myeloma was extremely desirable.

Myeloma Canada reemphasized that cilta-cel is a well understood therapy by patients and caregivers, but it is also an expensive and resource-intensive therapy. The survey responses indicate that access to cilta-cel is currently difficult for patients in Canada, leading some patients to seek treatment outside the country.

Clinician Input

Input From Clinical Experts Consulted for This Review

Unmet Needs

According to the clinical experts, the most important goal of treating patients with r/r MM is to control disease with minimal toxicities given there are currently no curative therapies. The clinical experts indicated that patients with MM commonly experience drug resistance to each line of therapy with progressively shorter durations of response. Additionally, experts highlighted that a treatment-free interval would be valuable for patients to improve their quality of life, given that current treatments often require injections weekly or even

twice a week, which are inconvenient for patients with MM. Therefore, the clinical experts stated that more treatment options working through novel pathways that can enhance and prolong treatment response with fewer side effects and improved convenience are needed.

Place in Therapy

The clinical experts indicated that cilta-cel would be an additional option for the management of patients with MM whose disease is refractory or exposed to lenalidomide. The clinical experts confirmed that the proposed place in therapy (i.e., second to fourth line) is reflective of anticipated clinical practice in Canada. In general terms, for patients who are eligible for transplant, the clinical experts considered a monoclonal antibody-based therapy (e.g., isatuximab-carfilzomib-dexamethasone or daratumumab-bortezomib-dexamethasone) as the preferred second-line treatment for patients whose disease is relapsing after lenalidomide-bortezomib-dexamethasone in the first line. Thus, cilta-cel may be preferred in the third or later line. Cilta-cel could be a preferred second-line treatment for a small percentage of patients (about 10%) such as those with higher genetic or disease risk and received daratumumab-lenalidomide-bortezomib-dexamethasone in the first line. For patients who are not eligible for transplant, according to the clinical experts, they would promote cilta-cel as a second-line treatment but noted that, in clinical practice, most patients (80% to 90%) would receive daratumumab-lenalidomide-dexamethasone as the first-line treatment, meaning they are not eligible for cilta-cel in the second line. The clinical experts would not limit access to cilta-cel by mandating trying other treatments first given exposure to cilta-cel earlier in a patient's disease course typically results in healthier and less exhausted T-cells.

Patient Population

The clinical experts confirmed that the patients included in the CARTITUDE-4 trial are generally reflective of the patient population with MM in clinical practice in Canada. According to the clinical experts, given there is no companion test required, or an established biomarker to identify those who may be most likely to benefit from cilta-cel, patients best suited for the treatment with cilta-cel would be identified by the professional judgment of physicians. Currently, as per feedback from the clinical experts, highly specialized testing, such as additional detailed genetic testing, is not widely available and not likely to become so anytime soon.

Assessing the Response to Treatment

The clinical experts stated that standard clinical assessments in urine, blood, scans, and bone marrow are used to document response or relapse. These assessments include urine and serum protein electrophoresis and immune fixation, serum free light chains, complete blood count, creatinine, calcium, and imaging (MRI, CT, PET-CT). The clinical experts mentioned that patient visits and blood assessments are usually done monthly initially, and then reduced to every 3 months for patients in remission and without symptoms. Imaging can be done annually or with the onset of new symptoms.

Discontinuing Treatment

As cilta-cel is a one-time treatment, the clinical experts indicated that discontinuation of treatment would not be relevant.

Prescribing Considerations

The clinical experts stated that cilta-cel should be administered in qualified institutions that are capable of properly managing patient cells, including acquisition, storage, and shipment. Additionally, the clinical experts indicated that specialized centres administering CAR T-cell therapy are required to have processes in place to manage acute toxicities occurring usually within the first 28 days after infusion, such as CRS, which needs intensive care unit availability, and neurotoxicity, which needs neurology availability. The management of patients with MM undergoing CAR T-cell therapy requires ongoing monitoring of immunity, revaccination, and immunoglobulin therapy administration according to the clinical experts.

Clinician Group Input

We received 2 clinician groups from OH-CCO Hematology Cancer Drug Advisory Committee, providing timely evidence-based clinical and health system guidance on drug-related issues in support of CCO's mandate, including the Provincial Drug Reimbursement Programs and the Systemic Treatment Program, and Canadian Myeloma Research Group (CMRG), a Canada-wide network of researchers aiming to develop better treatments for extending the life of patients with myeloma, enhancing the quality of life for those living with myeloma and related disorders, and working to find a cure for these diseases and other plasma cell disorders. Both groups gathered information by teleconference.

OH-CCO indicated that cilta-cel is an option as second-line treatment for patients who are eligible for transplant, or likely third-line treatment for patients who are not eligible for transplant as they would get daratumumab as a first-line treatment, and CMRG also emphasized that the availability of cilta-cel in the proposed setting would pertain primarily to patients who have had 2 prior lines; they may or may not have already received an anti-CD38 monoclonal antibody as well in the current treatment environment. CMRG further commented that the highest unmet need in myeloma continues to be adequate treatment for patients who have progressed despite exposure to effective drugs (e.g., triple-class refractory to an immunomodulatory drug, proteasome inhibitor, and anti-CD38 monoclonal antibodies) and with the movement of combinations of 3 major drug classes to the first- and second-line setting, exposure (and resistance) to multiple drug classes now occurs much earlier in the disease course. OH-CCO also mentioned that patients who were exposed to anti-CD38 monoclonal antibodies particularly had poorer outcomes.

OH-CCO considered that improved response, quality of life, disease-related symptoms, PFS, and OS are important outcomes. The CMRG highlighted that cilta-cel produces unprecedented rates of responses that are deeper compared to standard regimens; specifically, the rates of CR and stringent CR are between 70% to 75% compared to 20% with standard therapy.

Both groups agreed cilta-cel should be administered at tertiary hospitals or transplant centres with expertise in cellular therapy with an intensive care unit familiar with patients with cancer who are immunosuppressed, and an outpatient facility experienced in managing complex and urgent hematologic problems.

Drug Program Input

The clinical experts consulted for the review provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions From the Drug Programs

Drug program implementation questions	Clinical expert response
Relevant comparators	
The CARTITUDE-4 trial compared cilta-cel vs. physician's choice. Comparator therapies used in the CARTITUDE-4 trial included PVd or DPd. PVd is available as a comparator in Canada, but DPd is not funded. Other relevant funded comparators in Canada to cilta-cel depend on prior therapies used; these may include isatuximab-based triplets (e.g., IsaPd and IsaKd), SVd, DVd, KRd, and doublets with Pd and Kd.	This is a comment from the drug programs to inform pERC deliberations. The clinical experts mentioned that, for patients who are eligible for transplant, the relevant comparators are anti-CD38 combinations (daratumumab or isatuximab) with a proteasome inhibitor (carfilzomib or bortezomib). An anti-CD38-based combination would be used preferentially instead of pomalidomide or selinexor combinations. The currently funded anti-CD38 PI combinations are IsaKd and DVd. For patients who are not eligible for transplant and already treated with DRd, the options include SVd preferred, Kd and PVd, or PCd.
Considerations for initiation of therapy	
Given this reimbursement request would expand eligibility of CAR T cell for patients with multiple myeloma, if capacity limitations exist, how would you prioritize which patients are offered cilta-cel?	The clinical experts anticipated prioritizing patients with suitable prognostic factors who are likely to respond to the treatment and better able to tolerate side effects. The clinical experts noted that if difficult prioritization decisions need to be made, consideration could be given to patients for whom BCMA-directed therapies such as bispecific T-cell engagers would not be a suitable choice. The clinical experts would also prioritize those who live in remote communities, often requiring frequent long-distance journeys to receive continuous systemic treatment. pERC agreed with the clinical experts that local provincial governments should increase their ability to provide CAR T-cell therapies to patients. However, pERC noted that it is not the committee's mandate to decide the allocation of resources or prioritization of patients to receive treatment.
Patients enrolled in the CARTITUDE-4 trial were not permitted prior BCMA therapy (e.g., belantamab mafodotin, bispecific T-cell engagers). In clinical practice, should prior BCMA-directed therapy be an exclusion criterion to cilta-cel in this requested population?	pERC noted that the current review did not include any evidence to support the efficacy of cilta-cel in patients who had prior BCMA therapy. Therefore, the committee was unable to comment on the eligibility of these patients to receive cilta-cel.
Is there any evidence to support retreatment with CAR T cell? If yes, what is the appropriate time interval between initial CAR T cell and retreatment?	The CARTITUDE-4 trial excluded patients who had previously received CAR T-cell therapy or BCMA-targeted treatment. pERC noted that, at this time, CAR T-cell retreatment has not been established as an efficacious strategy and is not considered the standard of care.
Considerations for prescribing of therapy	
Access would be limited to jurisdictional capacity. The sponsor indicated that cilta-cel will be rolled out in 7 provinces. Currently, there are capacity limitations (e.g., health human resources, bed limitations). As more CAR T-cell products are implemented, it is anticipated that the capacity may not be able to meet the demand. Out-of-province or out-of-country care may still be needed. There may be issues with access and prolonged stay in (or near) specialized centres, especially for patients	This is a comment from the drug programs to inform pERC deliberations. The clinical experts stated that large increases in accredited specialized centres and staff are required to be able to offer this important therapy. In addition, significant education initiatives with roll-out will be required at both specialized and nonspecialized centres who may have to manage complications through emergency department visits, and so forth.

Drug program implementation questions	Clinical expert response
from remote areas. Financial support for travel and accommodation would be needed.	
Generalizability	
Patients enrolled in the CARTITUDE-4 trial had ECOG of 1 or less. Should patients with ECOG of 2 be eligible for cilta-cel after 1 to 3 prior lines of systemic therapy?	The CARTITUDE-4 trial enrolled patients with an ECOG performance status of 0 or 1. pERC agreed with the clinical experts that patients with an ECOG Performance Status of more than 1 may be treated at the discretion of the treating physician.
Funding algorithm (oncology only)	
Drug may change place in therapy of comparator drugs.	This is a comment from the drug programs to inform pERC deliberations.
Drug may change place in therapy of drugs reimbursed in previous lines.	This is a comment from the drug programs to inform pERC deliberations.
Drug may change place in therapy of drugs reimbursed in subsequent lines.	This is a comment from the drug programs to inform pERC deliberations.
Complex therapeutic space with multiple lines of therapy, subpopulations, or competing products.	This is a comment from the drug programs to inform pERC deliberations.
Care provision issues	
There will be significant resource use for patient preparation including leukapheresis, cell processing, and use of bridging and lymphodepleting chemotherapy. Specialized centres need to be trained and accredited by the sponsor. There is a high resource burden to obtain and maintain certification (including developing various protocols and supporting yearly audits). There is a need to coordinate patient care and product preparation with an external sponsor. There are now multiple CAR T-cell therapies being administered by specialized centres; managing various protocols for preparation and delivery of each product type poses an administrative burden.	This is a comment from the drug programs to inform pERC deliberations. pERC noted PAG's submission including the challenges with maintaining centre certification by FACT and observed that other than leukapheresis, centres do not undertake preparation of products for CAR T-cell therapies.
Is it safe to administer cilta-cel in the outpatient setting?	The clinical experts indicated that CRS and ICANS associated with cilta-cel therapy need immediate diagnosis and management; therefore, they would not consider administering cilta-cel in the outpatient setting. They noted that with time and experience, it may be possible to identify patients who are less likely to develop severe complications, such as grade 3 or 4 CRS, for whom treatment in an outpatient setting may be suitable. pERC agreed that it is safest to administer cilta-cel in specialized, inpatient settings. The committee acknowledged that each centre should determine whether it is safe and appropriate to administer cilta-cel on an outpatient basis. pERC also discussed that those who may qualify to receive cilta-cel as outpatients would need competent caregivers, raising considerations about access to caregiver support and potential burden on caregivers.

Drug program implementation questions	Clinical expert response
Additional resources (nursing, hospital bed, ICU) would be needed to treat adverse events. Resources would also be required outside the cancer system and need to be coordinated with the hospital.	This is a comment from the drug programs to inform pERC deliberations.
CAR T-cell therapies require availability and/or access to and potential increased use of supportive care agents; examples include growth factor support, cytokine-release syndrome agents (e.g., tocilizumab) and antimicrobials.	This is a comment from the drug programs to inform pERC deliberations.
System and economic issues	
This requested indication presents a significant expansion to the eligible population for CAR T cell for patients with multiple myeloma. The potential budget impact is extremely large and would be a significant increase. Costs related to out-of-country access may need to be considered from a system perspective.	This is a comment from the drug programs to inform pERC deliberations.
Cost of travel expenses for eligible patients would be needed.	This is a comment from the drug programs to inform pERC deliberations.
In some jurisdictions, the cost of CAR T cell may be borne through multiple sources and/or budgets, not just the drug programs.	This is a comment from the drug programs to inform pERC deliberations.
Cilta-cel received a conditionally positive recommendation for use in patients with multiple myeloma after 3 prior therapies. Negotiation is still active at the time of this input.	This is a comment from the drug programs to inform pERC deliberations.

BCMA = B-cell maturation antigen; CAR = chimeric antigen receptor; cilta-cel = ciltacabtagene autoleucel; CRS = cytokine-release syndrome; DPd = daratumumab-pomalidomide-dexamethasone; DRd = daratumumab-lenalidomide-dexamethasone; DVd = daratumumab-bortezomib-dexamethasone; ECOG = Eastern Cooperative Oncology Group; FACT = Foundation for the Accreditation of Cellular Therapy; ICANS = immune effector cell-associated neurotoxicity syndrome; ICU = intensive care unit; Isakd = isatuximab-carfilzomib-dexamethasone; IsaPd = isatuximab-pomalidomide-dexamethasone; Kd = carfilzomib-dexamethasone; KRd = carfilzomib-lenalidomide-dexamethasone; NA = not applicable; PAG = Provincial Advisory Group; PCd = pomalidomide-cyclophosphamide-dexamethasone; Pd = pomalidomide-dexamethasone; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; PI = proteasome inhibitor; PVd = pomalidomide-bortezomib-dexamethasone; SVd = selinexor-bortezomib-dexamethasone; vs. = versus.

Clinical Evidence

Description of Studies

One pivotal trial (CARTITUDE-4) was included in the systematic review. The CARTITUDE-4 trial is an ongoing phase III, open-label, randomized, multicentre study to evaluate efficacy and safety of cilta-cel compared to physician's choice of SOC therapies of either pomalidomide-bortezomib-dexamethasone or daratumumab-pomalidomide-dexamethasone in patients with r/r MM who have received 1 to 3 prior lines of therapy. The CARTITUDE-4 trial enrolled adults who had documented diagnosis of MM according to International Myeloma Working Group (IMWG) diagnostic criteria and had received 1 to 3 prior lines of therapy including a proteasome inhibitor and an immunomodulatory drug and were refractory to lenalidomide per IMWG consensus guidelines. A total of 419 eligible patients were randomized at a 1:1

ratio to receive either cilta-cel (n = 208) or standard therapy with pomalidomide-bortezomib-dexamethasone or daratumumab-pomalidomide-dexamethasone (n = 211). Randomization was stratified by investigator's choice of pomalidomide-bortezomib-dexamethasone or daratumumab-pomalidomide-dexamethasone, international staging system (ISS) at screening (I versus II versus III), and number of prior lines of therapy (1 versus 2 to 3). The median age of all study participants was 61.0 years with a range of 27 to 80 years. The demographic characteristics and disease history were balanced between treatment groups. At baseline, most of the participants were at ISS stage I (64.0%), had 2 lines of therapy (40.9%), had at least 1 high-risk cytogenetic abnormality (61.2%) with 1q gain or 1q amplification (47.0%) being the most reported abnormality. The primary objective of the study was to compare the efficacy of cilta-cel with SOC of either pomalidomide-bortezomib-dexamethasone or daratumumab-pomalidomide-dexamethasone in terms of PFS in patients with r/r MM and whose disease is refractory to lenalidomide. The primary end point was PFS according to a computerized algorithm per IMWG criteria, and secondary and other end points included CR or better rate, VGPR or better rate, ORR, MRD negativity rate, OS, duration of response (DOR), and HRQoL. The study was funded by Janssen and Legend Biotech.

Efficacy Results

Only those efficacy outcomes identified as important for this review were reported. Efficacy and safety data were evaluated at a planned interim analysis with data cut-off date of November 1, 2022.

Progression-Free Survival

In the interim analysis, 65 patients (31.3%) in the cilta-cel treatment group and 122 patients (57.8%) in the SOC group experienced an event. With a median follow-up of 15.8 months in the cilta-cel group, and 15.3 months in the SOC group, the median PFS was not reached (95% CI, 22.8 months to not estimable) for the cilta-cel group and was 11.8 months (95% CI, 9.7 months to 13.8 months) for the SOC group. The Kaplan-Meier estimate of PFS probabilities decreased from 75.9% (95% CI, 69.4% to 81.1%) to [redacted] in the cilta-cel group and 48.6% (95% CI, 41.5% to 55.3%) to [redacted] in the SOC group from 12 to 24 months. The PFS results were consistent across all prespecified and additional sensitivity analyses and subgroup results.

CR or Better Rate

The CR or better rate was higher in the cilta-cel group than the SOC group (73.1% versus 21.8% for cilta-cel versus SOC; OR = 10.3; 95% CI, 6.5 to 16.4; P < 0.0001).

VGPR or Better Rate

A total of 169 patients (81.3%) in the cilta-cel group and 96 patients (45.5%) in the SOC group reported a VGPR or better response (OR = 5.9; 95% CI, 3.7 to 9.4; nominal P < 0.0001).

Overall MRD Negativity Rate

A higher proportion of patients reported to have negative overall MRD by next-generation sequencing in the cilta-cel group compared to the SOC group in bone marrow (60.6% versus 15.6% for cilta-cel versus SOC; OR = 8.7; 95% CI, 5.4 to 13.9; P < 0.0001).

Overall Survival

With a median follow-up of 16.0 months for the cilta-cel group and 15.9 months for the SOC group, median OS was not reached in the cilta-cel group and was 26.7 month (22.5 to not estimable) in the SOC group. The Kaplan-Meier estimate of OS probabilities decreased from 84.1% (95% CI, 78.4% to 88.4%) [redacted] in the cilta-cel group and 83.6% (95% CI, 77.8% to 88.0%) [redacted] in the SOC group from 12 to 24 months.

Duration of Response

With a median follow-up of 13.7 months for the cilta-cel group and 14.3 months for the SOC group, the median DOR was not reached in the cilta-cel group and was 16.6 month (28.9 months to not estimable) in the SOC group. Among patients who had a partial response or better response (176 versus 142 for cilta-cel versus SOC), 143 patients (81.3%) in the cilta-cel group and 80 patients (56.3%) in the SOC group were censored. The Kaplan-Meier estimate of event-free probabilities decreased from 84.7% (95% CI, 78.1% to 89.4%) to [redacted] in the cilta-cel group and 63.0% (95% CI, 54.2% to 70.6%) to [redacted] in the SOC group from 12 to 24 months.

Time to Worsening of Symptoms in the Multiple Myeloma Symptom and Impact Questionnaire Total Symptom Score

The median time to a sustained worsening of MM symptoms was longer for the cilta-cel group (23.7 months) than the SOC group (18.9 months) with an HR of 0.42 (95% CI, 0.26 to 0.68; nominal P = 0.0003). The Kaplan-Meier estimate of event-free probabilities decreased from 84.6% (95% CI, 77.7% to 89.6%) to 79.8% (95% CI, 69.6% to 86.9%) in the cilta-cel group and 65.6% (95% CI, 55.2% to 74.2%) to 51.9% (95% CI, 34.5% to 66.8%) in the SOC group from 12 to 18 months.

Harms Results

All patients in both treatment groups reported at least 1 treatment emergent AE in the interim analysis (data cut-off was November 1, 2022). The most commonly reported AEs (i.e., reported by at least 20% of patients in either group) were: blood and lymphatic system disorders, including neutropenia (89.9% versus 85.1% for cilta-cel versus SOC), immune system disorders (77.5% versus 8.2%), gastrointestinal disorders (74.0% versus 55.8%), thrombocytopenia (54.3% versus 31.3%), and anemia (54.3% versus 26.0%). Serious AEs were reported among 44.2% of patients in the cilta-cel group and 38.9% of patients in the SOC group. Infections and infestations (24.0% versus 24.5%) including COVID-19 related pneumonia (5.8% versus 4.3%) was the most reported serious AE. Withdrawals due to treatment emergent AEs were reported among [redacted] in the cilta-cel group and [redacted] in the SOC group. The sponsor and/or the clinical experts identified notable harms include CRS, neurotoxicity (including immune effector cell-associated neurotoxicity syndrome [ICANS]), B-cell aplasia, hypogammaglobulinemia, and immune suppression. CRS was reported for 76.1% patients in the cilta-cel group (134 of 176 patients who received cilta-cel as study treatment), with the majority being grade 1 (52.8%). Only 2 patients (1.1%) experienced grade 3 CRS, and no grade 4 or 5 CRS was reported. In total, 36 patients (20.5%) from the cilta-cel group experienced CAR T-cell neurotoxicity, including ICANS in 8 patients (4.5%). Among the 8 patients with ICANS, 6 patients (3.4%) had grade 1 events and 2 patients (1.1%) had grade 2 events.

Hypogammaglobulinemia was observed in 88 of 202 patients (42.3%) in the cilta-cel group and 13 of 202 patients (6.3%) in the SOC group, with 15 patients (7.2%) in the cilta-cel group and 1 patient (0.5%) in the SOC group experienced grade 3 or 4 hypogammaglobulinemia. Immune suppression was observed in 186 patients (89.4%) in the cilta-cel group and 182 patients (87.5%) in the SOC group. No data for B-cell aplasia were reported.

Critical Appraisal

In the CARTITUDE-4 trial, at baseline, higher proportions of patients received concomitant antimicrobial and antiviral medications, normal human immunoglobulin, serotonin (5-HT3) antagonists, paracetamol, and enoxaparin in the cilta-cel group than the SOC group, some of which might have had an impact on the frequency of reported AEs in the cilta-cel group. Additionally, patients in the cilta-cel group reported more frequent concomitant use of interleukin inhibitors than the SOC group. According to the clinical experts, interleukin inhibitors are immunosuppressants, which could decrease T-cell function, which may bias the efficacy results against cilta-cel. Fewer patients received subsequent anticancer treatment in the cilta-cel group than the SOC group; the review team agreed with the clinical experts that this would bias the subsequent OS results against cilta-cel. A higher proportion of patients in the cilta-cel group discontinued treatment than the SOC group (for cilta-cel versus SOC). The review team noted that the differential imbalance in the baseline characteristics of the patients who discontinued treatment between the 2 groups could be a source of attrition bias against the cilta-cel group.

As the CARTITUDE-4 trial is ongoing, results were only available in the interim analysis (data cut-off of November 1, 2022), and the median PFS and median OS were not reached in the cilta-cel group at the time of the interim analysis. Although results from the sponsor-conducted subsequent OS analysis (data cut-off of December 13, 2023) indicated a trend favouring OS benefit for the cilta-cel group compared to the SOC group, the median OS was still not yet reached at this time. The statistical testing of the subsequent OS analysis was not controlled for the overall type I error; therefore, the results were descriptive and should be considered as supportive data. Many of the outcomes used in the CARTITUDE-4 trial (PFS, OS, CR or better rate, VGPR or better rate, ORR, and DOR) were identified as clinically important by patients and/or clinicians; however, VGPR or better rate and DOR were not part of the statistical testing strategy and were not adjusted for multiple testing. Therefore, the ability to provide conclusions from these data may be limited.

It is uncertain the extent to which the observed OS, patient reported HRQoL, and disease symptom results from the CARTITUDE-4 trial could be generalized to clinical practice in Canada considering the limited representativeness of the study population due to restrictive eligibility criteria and comparators. The eligibility criteria for the CARTITUDE-4 trial excluded a small group of patients (less than 5%) with symptomatic MM who did not have measurable disease and patients with ECOG of 2. The clinical experts opined that those patients would not necessarily be excluded from eligibility for cilta-cel. The clinical experts noted that patients who have a confirmed disease that relapsed, even if nonsecretory, may still benefit from therapy with cilta-cel. Patients with ECOG Performance Status of 2, especially if the poor performance score is due to myeloma disease burden, may also benefit. Careful consideration of overall health and ability to withstand acute toxicities such as CRS would be important. The comparators used in the trial (i.e., pomalidomide-

bortezomib-dexamethasone and daratumumab-pomalidomide-dexamethasone) may not exactly be reflective of the current clinical practice in Canada and there was no study site in Canada in the CARTITUDE-4 trial. However, comparable triplet regimens are used, thus findings are relevant to clinical practice in Canada. Patient and clinician groups indicated that prolonging PFS and OS, delaying progression, maintaining HRQoL, and controlling the symptoms of the disease were critical treatment considerations.

GRADE Summary of Findings and Certainty of the Evidence

GRADE was used to assess the certainty of the evidence for outcomes considered most relevant to inform expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group.[12,13] Following the GRADE approach, evidence from randomized controlled trials started as high-certainty evidence and could be rated down for concerns related to study limitations (internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias.

The selection of outcomes for GRADE assessment was based on the sponsor's summary of clinical evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members: PFS, CR or better rate, VGPR or better rate, overall MRD negativity rate, OS, DOR, HRQoL, and serious AEs. As per feedback from the clinical experts, ORR was not selected in the GRADE assessment as it represents patients with any type of response, which may not be as informative as CR or better rate and VGPR or better rate in terms of providing clinically relevant information as an efficacy outcome.

Table 3: Summary of Findings for Cilta-Cel Versus SOC for Patients With r/r MM

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects			Certainty	What happens
			SOC	Cilta-cel (95% CI)	Difference (95% CI)		
Progression-free survival							
Probability of being alive and progression-free at 12 months Follow-up (median): Cilta-cel: 15.8 months SOC: 15.3 months	419 (1 RCT)	NR	486 per 1,000	759 per 1,000 (694 to 811 per 1,000)	[redacted])	Moderate[a]	Cilta-cel likely results in a clinically important higher probability of patients being alive and progression-free at 12 months compared with SOC.
Probability of being alive and progression-free at 24 months Follow-up (median):	419 (1 RCT)	NR	[redacted]	[redacted]	NA[b]	Moderate[a]	Cilta-cel likely results in a clinically important higher probability of patients being alive and progression-free at 24 months compared with SOC.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects			Certainty	What happens
			SOC	Cilta-cel (95% CI)	Difference (95% CI)		
Cilta-cel: 15.8 months SOC: 15.3 months							
Overall best confirmed response							
The proportion of patients who achieved a CR or sCR response Follow-up (median): Cilta-cel: 15.8 months SOC: 15.3 months	419 (1 RCT)	OR = 10.3 (6.5 to 16.4)	218 per 1,000	731 per 1,000 (665 to 790 per 1,000)	[redacted]	High[c]	Cilta-cel results in an increase in CR or better rate compared with SOC. The clinical importance of the increase is unclear.
The proportion of patients who achieved a CR, sCR, or VGPR response Follow-up (median): Cilta-cel: 15.8 months SOC: 15.3 months	419 (1 RCT)	[redacted]	[redacted]	[redacted]	[redacted]	High[c,d]	Cilta-cel results in an increase in VGPR or better rate compared with SOC. The clinical importance of the increase is unclear.
Overall MRD negativity rate at 10^{-5} in bone marrow							
The proportion of patients who achieved overall MRD negative status (at 10^{-5}) Follow-up (median): Cilta-cel: 10.9 months SOC: 12.3 months	419 (1 RCT)	OR = 8.7 (5.4 to 13.9)	156 per 1,000	606 per 1,000 (536 to 673 per 1,000)	[redacted]	High[c]	Cilta-cel results in an increase in overall MRD negativity rate compared with SOC. The clinical importance of the increase is unclear.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects			Certainty	What happens
			SOC	Cilta-cel (95% CI)	Difference (95% CI)		
Overall survival							
Probability of being alive at 12 months Follow-up (median): Cilta-cel: 16.0 months SOC: 15.9 months	419 (1 RCT)	NR	836 per 1,000	841 per 1,000 (784 to 884 per 1,000)		Moderate[e]	Cilta-cel likely results in little to no difference in the probability of being alive at 12 months.
Probability of being alive at 24 months Follow-up (median): Cilta-cel: 16.0 months SOC: 15.9 months	419 (1 RCT)	NR			NA[a]	Moderate[e]	Cilta-cel likely results in little to no difference in the probability of being alive at 24 months.
Duration of response							
Probability of remaining in response (CR, sCR, VGPR, or PR) at 12 months Follow-up (median): Cilta-cel: 13.7 months SOC: 14.3 months	419 (1 RCT)	NR	630 per 1,000	847 per 1,000 (781 to 894 per 1,000)		High[c]	Cilta-cel results in an increase in the probability of remaining in response (CR, sCR, VGPR, or PR) at 12 months compared with SOC. The clinical importance of the increase is unclear.
Probability of remaining in response (CR, sCR, VGPR, or PR) at 24 months Follow-up (median): Cilta-cel: 13.7 months SOC: 14.3 months	419 (1 RCT)	NR			NA[a]	High[c,f]	Cilta-cel results in an increase in the probability of remaining in response (CR, sCR, VGPR, or PR) at 24 months compared with SOC. The clinical importance of the increase is unclear.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects			Certainty	What happens
			SOC	Cilta-cel (95% CI)	Difference (95% CI)		
Health-related quality of life							
Probability of having subsequent improvement in the MySIm-Q total symptom score at 12 months Follow-up (median): Cilta-cel: 12.4 months SOC: 12.0 months	419 (1 RCT)	NR	656 per 1,000	846 per 1,000 (777 to 896 per 1,000)	[redacted]	Moderate[c,g]	Cilta-cel likely results in an increase in the probability of having subsequent improvement in the MySIm-Q total symptom score at 12 months compared with SOC. The clinical importance of the increase is unclear.
Probability of having subsequent improvement in the MySIm-Q total symptom score at 18 months Follow-up (median): Cilta-cel: 12.4 months SOC: 12.0 months	419 (1 RCT)	NR	[redacted]	[redacted]	[redacted]	Moderate[c,g]	Cilta-cel likely results in an increase in the probability of having subsequent improvement in the MySIm-Q total symptom score at 18 months compared with SOC. The clinical importance of the increase is unclear.
Serious adverse event							
Proportion of patients with at least 1 SAE Follow-up (median): Cilta-cel: NR SOC: NR	416 (1 RCT)	NR	389 per 1,000	442 per 1,000 (NR)	[redacted]	Low[h]	Cilta-cel may result in little to no difference in the proportion of patients with at least 1 SAE compared with SOC.

Cilta-cel = ciltacabtagene autoleucel; CI = confidence interval; CR = complete response; DOR = duration of response; MID = minimal important difference; HRQoL = health-related quality of life; MRD = minimal residual disease; MySIm-Q = Multiple Myeloma Symptom and Impact Questionnaire; NA = not available; NR = not reported; OR = odds ratio; OS = overall survival; PFS = progression-free survival; PR = partial response; RCT = randomized controlled trial; r/r MM = relapsed or refractory multiple myeloma; sCR = stringent complete response; SAE = serious adverse event; SOC = standard of care; VGPR = very good partial response; vs. = versus.

Note: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

[a]Rated down 1 level for serious imprecision. There is no established between-group MID for PFS at 12 months, but the clinical experts considered that a 20% difference between groups in the probability of patients being alive and progression-free could be considered a threshold of clinical importance. The point estimate and the upper bound of the 95% CI for the between-group difference suggested a clinically important difference for cilta-cel vs. SOC based on a 20% threshold while the lower bound of the 95% CI suggested no clinically important difference between the 2 groups. In the absence of available data for the between-group difference in PFS probabilities at 24 months, the judgment of imprecision was based on the point estimates per different groups using the null as the threshold. The clinical importance of the between-group difference was judged based on the input of the clinical experts and the observed trend of differences, which was consistent with that of at 12 months.

[b]The estimates of between-group difference were not available. The sponsor indicated that the 24-month PFS, OS, and DOR data were immature given the median follow-up of the study duration was 15.9 months at the interim analysis.

[c]Imprecision was not rated down. There is no established MID, and the clinical experts could not provide a threshold of important difference, thus the target of certainty appraisal was any effect for the outcome.

[d]The statistical testing for VGPR or better rate was not adjusted for multiplicity in the CARTITUDE-4 trial and should be considered as supportive evidence.

[e]Rated down 1 level for serious imprecision. There is no established MID, and the clinical experts could not provide a threshold of important difference, thus target of certainty appraisal was any effect for OS. At 12 months, the lower bound of the 95% CI for the between-group difference was less than 0 while the upper bound was more than 0, suggesting no clinically important difference between the 2 groups. At 24 months, given the between-group difference in OS probabilities was not available due to the immaturity of data as indicated by the sponsor, the judgment of imprecision was based on the point estimates per different groups using the null as the threshold and the observed trend of differences, which was similar to that of at 12 months.

[f]Imprecision was not rated down. There is no established MID, and the clinical experts could not provide a threshold of important difference, thus target of certainty appraisal was any effect for the outcome. In the absence of available data for the between-group difference in the probability of remaining in response (CR, sCR, VGPR, or PR) at 24 months, the judgment of imprecision was based on the point estimates per different groups using the null as the threshold.

[g]Rated down 1 level for serious risk of bias. There were consistently and notably higher proportions of patients in the cilta-cel group than SOC group who received various concomitant therapies for the control of various clinical symptoms or disorders associated with the increased incidence of adverse events. Given the frequency and/or severity of the adverse events that might significantly affect patients' HRQoL including daily functions, the imbalances in concomitant medications may bias the HRQoL results in favour of cilta-cel.

[h]Rated down 2 levels for very serious imprecision. There is no established MID and clinical experts suggested that 10% is the threshold of important difference in the proportion of patients with at least 1 SAE. The point estimate and lower bound of the 95% CI for the between-group difference suggested no clinically important difference between the groups; the upper bound of the 95% CI for difference between groups suggested a clinically important harm of cilta-cel.

Source: 2023 primary clinical study report for cartitude-4 and sponsor provided additional data. details included in the table are from the sponsor's summary of clinical evidence.

Long-Term Extension Studies

No long-term extension studies were submitted for this review.

Indirect Comparisons

Description of Studies

Two reports of ITC analyses were submitted by the sponsor. One ITC report was based on the IPTW analyses, in which individual patient data from daratumumab trials including CANDOR (carfilzomib-dexamethasone), CASTOR (bortezomib-dexamethasone, daratumumab-bortezomib-dexamethasone), and APOLLO (pomalidomide + dexamethasone) were matched to eligibility criteria of the CARTITUDE-4 trial, to inform the comparison to cilta-cel. Another ITC report presented unanchored MAIC analyses, matching individual patient data from the cilta-cel group of the CARTITUDE-4 trial to isatuximab + pomalidomide + dexamethasone group of the ICARIA-MM trial and selinexor + bortezomib + dexamethasone group of the BOSTON trial. The comparative treatment effect on outcomes of interest were reported, including tumour response outcomes (ORR, VGPR or better, CR or better) and survival outcomes (PFS and OS). Base-case scenario for tumour response and PFS outcomes incorporated 4 variables in the IPTW analyses (refractory status, ISS disease stage, presence of plasmacytomas or extramedullary disease, time to progression in prior line) and 3 variables (refractory status, cytogenetic risk, ISS disease stage) in MAIC analyses. Assessment of OS was conducted by multivariable regression with 14 prognostic variables used for adjustment.

In the IPTW analyses, the CARTITUDE-4 study data excluded patients with prior anti-CD38 therapy, leading to a sample size of 155 patients for the comparative analyses. The comparator treatment populations consisted of the following cohorts: 44 patients treated with daratumumab-bortezomib-dexamethasone (CASTOR trial), 46 patients treated with bortezomib-dexamethasone (CASTOR trial), 46 patients treated with carfilzomib-dexamethasone (CANDOR trial), and 92 patients treated with pomalidomide + dexamethasone (APOLLO trial).

In the MAIC analysis, the CARTITUDE-4 study initially consisted of 208 patients who were treated with cilta-cel. The number of patients in the isatuximab + pomalidomide + dexamethasone and selinexor + bortezomib + dexamethasone cohorts were 154 and 53, respectively. Following the MAIC adjustment, the cilta-cel effective sample size was 26 for the comparison to isatuximab + pomalidomide + dexamethasone (ICARIA-MM trial), and 188 for the comparison to selinexor + bortezomib + dexamethasone (BOSTON trial).

Efficacy Results

Progression-Free Survival

IPTW-Based Analyses

The observed median PFS for cilta-cel was not reached. The observed median PFS was 7.59 months (95% CI, 6.51 to 11.17) for daratumumab-bortezomib-dexamethasone, 4.93 months (95% CI, 3.98 to 6.57) for bortezomib-dexamethasone, 12.01 months (95% CI, 7.43 to 15.26) for carfilzomib-dexamethasone, and 6.93 months (95% CI, 4.73 to 9.53) for pomalidomide + dexamethasone, respectively. The median PFS using IPTW weighting was 9.79 months (95% CI, 6.51 to 13.40) for daratumumab-bortezomib-dexamethasone, 6.21 months (95% CI, 3.84 to 7.03) for bortezomib-dexamethasone, 11.09 months (95% CI, 3.98 to 15.26) for carfilzomib-dexamethasone, and 8.34 months (95% CI, 2.14 to 9.26) for pomalidomide + dexamethasone.

Following IPTW adjustment, the conditional HR for PFS between cilta-cel and carfilzomib-dexamethasone was 0.27 (95% CI, 0.16 to 0.45), between cilta-cel and pomalidomide + dexamethasone was 0.19 (95% CI, 0.13 to 0.30), between cilta-cel and bortezomib-dexamethasone was 0.11 (95% CI, 0.07 to 0.17), and between cilta-cel and daratumumab-bortezomib-dexamethasone was 0.25 (95% CI, 0.15 to 0.41), all favouring cilta-cel.

Unanchored MAIC Analyses

The median adjusted PFS for cilta-cel was not reached. The median PFS for isatuximab + pomalidomide + dexamethasone and selinexor + bortezomib + dexamethasone were [redacted] and [redacted]), respectively.

MAIC-adjusted HR for PFS between treatment groups was 0.32 (95% CI, 0.15 to 0.70) in the cilta-cel versus isatuximab + pomalidomide + dexamethasone comparison and [redacted]) in the cilta-cel versus selinexor + bortezomib + dexamethasone comparison.

Overall Survival

IPTW-Based Analyses

The observed median OS for cilta-cel and carfilzomib-dexamethasone was not reached. The observed median OS for daratumumab-bortezomib-dexamethasone, bortezomib-dexamethasone, and pomalidomide + dexamethasone was [redacted], and [redacted], respectively.

Following adjustment, the conditional HR for OS between cilta-cel and carfilzomib-dexamethasone was [redacted] between cilta-cel and pomalidomide + dexamethasone was [redacted]), between cilta-cel and bortezomib-dexamethasone was [redacted]), and between cilta-cel and daratumumab-bortezomib-dexamethasone was [redacted]).

Unanchored MAIC Analyses

The median OS for cilta-cel was not reached. Median OS for isatuximab + pomalidomide + dexamethasone and selinexor + bortezomib + dexamethasone were [redacted] and [redacted], respectively. Adjusted HR for OS was [redacted] in the cilta-cel versus isatuximab + pomalidomide + dexamethasone comparison and [redacted] in the cilta-cel versus selinexor + bortezomib + dexamethasone comparison.

Overall Response Rate

IPTW-Based Analyses

Observed ORR in the treatment populations were 89.7% for cilta-cel, 76.1% for carfilzomib-dexamethasone, 42.4% for pomalidomide + dexamethasone, 54.4% for bortezomib-dexamethasone, and 72.7% for daratumumab-bortezomib-dexamethasone. The IPTW-estimated relative risks (RRs) were 1.32 (95% CI, 0.99 to 1.74) for cilta-cel versus carfilzomib-dexamethasone, 2.00 (95% CI, 1.31 to 3.06) for cilta-cel versus pomalidomide + dexamethasone, 1.77 (95% CI, 1.19 to 2.65) for cilta-cel versus bortezomib-dexamethasone, and 1.38 (95% CI, 0.86 to 2.20) for cilta-cel versus daratumumab-bortezomib-dexamethasone.

Unanchored MAIC Analyses

Observed proportions in the treatment populations were 84.6% for cilta-cel, 60.4% for isatuximab + pomalidomide + dexamethasone, and [redacted] for selinexor + bortezomib + dexamethasone. The MAIC-estimated RRs were 1.39 (95% CI, 1.19 to 1.63) for cilta-cel versus isatuximab + pomalidomide + dexamethasone, and [redacted] for cilta-cel versus selinexor + bortezomib + dexamethasone.

CR or Better

IPTW-Based Analyses

Observed proportions in the treatment populations were 78.1% for cilta-cel, 10.9% for carfilzomib-dexamethasone, 2.2% for pomalidomide + dexamethasone, 4.4% for bortezomib-dexamethasone, and 11.4% for daratumumab-bortezomib-dexamethasone. The IPTW-estimated RRs were 6.48 (95% CI, 2.72 to 15.43) for cilta-cel versus carfilzomib-dexamethasone, 38.76 (95% CI, 8.55 to 175.8) for cilta-cel versus pomalidomide + dexamethasone, 15.60 (95% CI, 3.88 to 62.73) for cilta-cel versus bortezomib-dexamethasone, and 9.36 (95% CI, 3.35 to 26.14) for cilta-cel versus daratumumab-bortezomib-dexamethasone.

Unanchored MAIC Analyses

Observed proportions in the treatment populations were 73.1% for cilta-cel, 4.5% for isatuximab + pomalidomide + dexamethasone, and 9.4% for selinexor + bortezomib + dexamethasone. The MAIC-estimated RRs were 17.30 (95% CI, 8.29 to 36.11) for cilta-cel versus isatuximab + pomalidomide + dexamethasone, and [redacted] for cilta-cel versus selinexor + bortezomib + dexamethasone.

VGPR or Better

IPTW-Based Analyses

Observed VGPR or better in the treatment populations were 85.2% for cilta-cel, 52.2% for carfilzomib-dexamethasone, 14.1% for pomalidomide + dexamethasone, 15.2% for bortezomib-dexamethasone, and 40.9% for daratumumab-bortezomib-dexamethasone. The IPTW-estimated RRs were 1.81 (95% CI, 1.24 to 2.64) for cilta-cel versus carfilzomib-dexamethasone, 3.73 (95% CI, 1.52 to 9.15) for cilta-cel versus pomalidomide + dexamethasone, 5.13 (95% CI, 2.39 to 10.99) for cilta-cel versus bortezomib-dexamethasone, and 2.51 (95% CI, 1.39 to 4.53) for cilta-cel versus daratumumab-bortezomib-dexamethasone.

Unanchored MAIC Analyses

Observed VGPR or better in the treatment populations were 81.3% for cilta-cel, 31.8% for isatuximab + pomalidomide + dexamethasone, and [redacted] for selinexor + bortezomib + dexamethasone. The MAIC-estimated RRs were 2.52 (95% CI, 1.95 to 3.25) for cilta-cel versus isatuximab + pomalidomide + dexamethasone, and [redacted] for cilta-cel versus selinexor + bortezomib + dexamethasone.

Harms Results

Sponsor-conducted ITCs did not evaluate comparative safety of cilta-cel.

Critical Appraisal

The sponsor-conducted IPTW analyses demonstrated favourable benefits of cilta-cel relative to carfilzomib-dexamethasone, pomalidomide + dexamethasone, bortezomib-dexamethasone, and daratumumab-bortezomib-dexamethasone treatments, though important limitations were noted. Heterogeneity between

the CARTITUDE-4 trial and the comparator trials was observed, both in terms of study eligibility criteria and baseline population characteristics. Reduced sample sizes were generated and used in the analyses, after matching and adjustment methods. Certain prognostic factors, such as cytogenetic risk and type of previous treatment regimen, were unavailable for the adjustment in the IPTW analyses. Further uncertainty is associated with the possibility of unknown, unmeasured, or unmeasurable confounders, which cannot be accounted from propensity score methods. Regarding the assessment of survival outcomes, median PFS and OS were not reached for cilta-cel, and there was evidence of a possible violation of proportional hazard assumptions for certain comparisons (i.e., possible visual violation observed for daratumumab-bortezomib-dexamethasone, carfilzomib-dexamethasone, and pomalidomide + dexamethasone comparisons [PFS outcome] and carfilzomib-dexamethasone comparison [OS outcome]; statistical violation, based on the Grambsch-Therneau test, observed for bortezomib-dexamethasone comparison [PFS outcome]). Input from the clinical expert suggested that certain important treatments of interest for clinical practice in Canada (isatuximab-carfilzomib-dexamethasone) were missing in the ITC analyses. Moreover, comparative safety and HRQoL were not evaluated, despite being considered important outcomes for patients with MM. It is likely that the IPTW estimates are subject to an unknown amount and direction of bias.

Limitations of the sponsor-conducted unanchored MAIC included restrictions in effective sample sizes of cilta-cel, following MAIC adjustments, and notable heterogeneity in prognostic and effect modifying factors across the individual studies. The exploration of between study differences was further limited by missing information on patient characteristics across the trials. Generalizability issues are associated with diverse eligibility criteria between the comparator and cilta-cel cohorts, mainly inclusion of patients with ECOG of 0,1, and 2 in the BOSTON trial and inclusion of patients with at least 2 previous lines of treatment in the ICARIA-MM trial. Thus, concerns remain that not all prognostic and effect modifying factors were accounted in the unanchored comparisons, leading to challenges to interpretation and high uncertainty of MAIC findings.

Studies Addressing Gaps in the Evidence From the Systematic Review

No studies addressing gaps in the systematic review evidence were submitted for this review.

Ethical Considerations

Patient and clinician group and drug program input, as well as consultation with clinical experts and clinical and economic reviewers were reviewed to identify ethical considerations specific to the use of cilta-cel for the treatment of adult patients with MM, who have received 1 to 3 prior lines of therapy, including a proteasome inhibitor and an immunomodulatory drug, and whose disease is refractory to lenalidomide:

- **Patient experiences and treatment options for MM:** As described in detail in the Clinical Review report, MM is a hematological malignancy for which there are currently no available curative treatments. Patients with MM undergo successive lines of therapy, with progressively worsening outcomes, and eventually develop refractory disease. Treatment for MM is considered continuous, requiring frequent (even weekly) treatment and monitoring, and offers no treatment-free windows. MM and its treatment are physically, psychosocially, and financially burdensome for patients and

caregivers. Clinical experts noted that the treatment and monitoring requirements for MM are additionally burdensome for patients living in rural or remote communities (including First Nations, Inuit, and Métis communities) who must travel to access treatment.

- **Evidentiary uncertainties related to cilta-cel for MM:** The safety and efficacy of cilta-cel compared to physician's choice of SOC therapies (either pomalidomide-bortezomib-dexamethasone or daratumumab-pomalidomide-dexamethasone) in the treatment of adult patients with r/r MM who have received 1 to 3 prior lines of therapy was evaluated in the pivotal, ongoing phase III, open-label, randomized CARTITUDE-4 trial. As noted in the Clinical Review report, treatment with cilta-cel demonstrated a clinically significant benefit in terms of the primary end point of PFS compared to SOC of pomalidomide-bortezomib-dexamethasone or daratumumab-pomalidomide-dexamethasone. However, the OS benefit was uncertain due to immaturity of the data. Additionally, as noted by the clinical experts, the SOC comparators used in the trial may not reflect current clinical practice in Canada, which may impact the generalizability of the results. Comparative evidence for other, relevant comparators (carfilzomib-dexamethasone, pomalidomide + dexamethasone, bortezomib-dexamethasone, daratumumab-bortezomib-dexamethasone, isatuximab + pomalidomide + dexamethasone, and selinexor + bortezomib + dexamethasone) was submitted through 2 ITC reports. The Clinical Review report concluded that cilta-cel demonstrated a statistically significant improvement in OS and progression PFS relative to currently available therapies (with the exception of no statistically significant differences in terms of OS when compared with carfilzomib-dexamethasone and isatuximab + pomalidomide + dexamethasone). However, the Clinical Review report noted that the ITCs had methodological limitations, which added uncertainty to the OS and PFS benefits estimated in the ITCs. The clinical experts noted that more comparative evidence was required to determine whether the risk-benefit favoured CAR T cell for use in patients who were eligible for transplant and had yet to undergo transplant or treatment with an anti-CD38 drug. The CARTITUDE-4 trial did not yield long-term safety and efficacy data. Clinical experts noted the need for long-term data on safety, efficacy, and comparative effectiveness (including with emerging therapeutic options such as other BCMA-targeting drugs such as bispecific antibodies), especially for use of cilta-cel in earlier lines of treatment with existing therapeutic options. Together, the uncertainties in comparative effectiveness and long-term effectiveness and safety have ethical implications for informed consent. Uncertainty about the long-term safety, efficacy, and comparative effectiveness also presents challenges for pharmacoeconomic assessments and has prompted consideration of alternative pricing and reimbursement models. Although not used in Canada to-date, the sponsor has indicated that they are preparing the groundwork to enable value-based reimbursement for cilta-cel. Notably, how risk-sharing arrangements are designed (e.g., chosen parameters) has ethical implications for the distribution of their potential benefits and burdens between patients, the public, payers, and sponsors.
- **Risk of secondary T-cell lymphomas:** CAR T-cell therapies including cilta-cel may pose a rare, class-level risk of secondary malignancy of developing CAR-positive T-cell lymphoma. Although the development of CAR-positive T-cell lymphoma was not observed in the CARTITUDE-4 trial, clinical experts acknowledged the possibility of this risk with cilta-cel. However, they suggested that, based

on currently available evidence, this risk would not alter their decision-making regarding cilta-cel as both MM and existing therapies for MM also posed the risk of secondary malignancies. Clinical experts noted the importance of informing patients of this risk, which requires life-long monitoring as described in the product monograph, during consent conversations.

- **Clinical decision-making for r/r MM:** Patient and clinician group input highlighted that patients' goals include the desire for a one-time, life-extending therapy that does not require active management given the unmet need for curative treatment and burdensome nature of existing therapies. Clinical experts noted that patients residing in rural or remote communities might especially benefit from a one-time therapy such as cilta-cel, including in earlier lines of therapy, given the expected reduction in need for frequent travel associated with accessing alternate treatments for MM. Clinical experts also noted that introducing cilta-cel in earlier lines of therapy for MM increased the complexity of prioritizing patients in the context of capacity constraints. They described that prescribing decisions would require considering availability and comparative evidence for other therapeutic options in second- and third-line treatments (including opportunities to access other BCMA-targeting agents in the future), whether CAR T-cell therapy would be more effective in earlier lines of therapy while patients have less pretreated disease, and a patient's individual presentation of the disease and circumstances.
- **Implications of capacity constraints for the use of cilta-cel in earlier lines of therapy for MM:** Clinical experts emphasized that offering cilta-cel for MM, especially in earlier lines of therapy, would require increasing delivery capacity in Canada. They reiterated that Canada still lacks sufficient health systems capacity to deliver CAR T-cell therapy to all eligible patients, given the resource-, personnel-, and infrastructure-intensive nature of CAR T-cell therapy. They noted that insufficient human resources, including hematological specialists skilled in monitoring and responding to acute toxicities, could limit safe and effective delivery of CAR T-cell therapy. There are ethical, equity, and access challenges arising from existing limitations in manufacturing and delivery capacity for CAR T-cell therapy. Clinical experts cautioned that in the absence of sufficient capacity to deliver CAR T-cell therapy to all eligible patients and in the absence of transparent, fair guidance on how to prioritize patients for access to limited therapy, reimbursement of cilta-cel may contribute to inequitable access to treatment (e.g., favouring patients residing near treatment centres or those who are more vocal). Recognizing and mitigating structural and systemic factors that may impact a patients' perceived priority or eligibility can help support equitable access. Clinical experts also reiterated the importance of offering support for patients and caregivers who reside in rural or remote communities to reduce geographic and financial barriers to equitable access. The sponsor has indicated that they are currently developing and discussing a patient support program with payers and pan-Canadian Pharmaceutical Alliance for cilta-cel in the fourth line. The program is proposed to address gaps jurisdictional or centre-based support for education and travel and accommodation-associated costs for patients and caregivers for apheresis and infusion, but the sponsor acknowledged the regional inequalities may remain.

Economic Evidence

Cost and Cost-Effectiveness

Table 4: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis, partitioned survival model
Target population	Adult patients with MM, who have received 1 to 3 prior lines of therapy, including a proteasome inhibitor and an immunomodulatory drug, and whose disease is refractory to lenalidomide
Treatment	Cilta-cel
Dose regimen	0.5 to 1.0 × 10^6 CAR-positive viable T-cells per kilogram of body weight, with a maximum dose of 1 × 10^8 CAR-positive viable T-cells per single infusion
Submitted price	$632,455 per administration
Submitted treatment cost	$632,455 per patient as a one-time infusion
Comparators	Kd, Pd, IsaPd, IsaKd (included in a scenario analysis only), Vd, DVd, SVd
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (40 years)
Key data source	Efficacy for cilta-cel informed by the CARTITUDE-4 trial; efficacy for comparators was informed by sponsor-submitted indirect treatment comparisons
Submitted results	Compared to Vd, cilta-cel was associated with an ICER of $69,861 per QALY gained. Based on the sequential analysis, 3 treatments (Pd, Vd, and cilta-cel) were on the cost-effectiveness perimeter.
Key limitations	• In the interim analysis (data cut-off of November 11, 2022) of the CARTITUDE-4 trial, median PFS and OS was not reached. In the absence of robust long-term data, PFS and OS beyond the trial data for cilta-cel is uncertain. The sponsor's extrapolation of OS for patients receiving cilta-cel was deemed inappropriate as the survival analysis was conducted on a population with heterogenous rates of survival. This led to the assumption that the risk of mortality would continue to rapidly decline over time, despite no long-term evidence to support this. This overestimated the LY gains associated with cilta-cel, leading to the conclusion that cilta-cel would be curative for approximately 37% of patients who received it. There is no available evidence that cilta-cel is curative in the indicated population. • Evidence from the CARTITUDE-4 trial only compared cilta-cel against treatments that are not frequently used in Canada for the indicated population. The comparative efficacy of cilta-cel vs. relevant comparators is uncertain due to an absence of head-to-head clinical trials and limitations with the sponsor-conducted indirect treatment comparisons. • The sponsor applied the same subsequent therapy costs as a one-off cost to all comparators when a patient enters the postprogression health state; this was considered inappropriate. Clinical expert feedback we received noted that subsequent therapies are dependent on a patient's prior therapy. The model structure does not allow multiple subsequent therapies to be modelled and therefore an accurate assessment of subsequent therapy costs could not be estimated. • The treatment schedule for Kd was not reflective of clinical practice in Canada. The sponsor used twice-weekly dosing for estimating costs and health outcomes for Kd; however, most centres in Canada use once-weekly dosing. Since weekly dosing is associated with lower costs and better efficacy, the cost of the Kd regimen was overestimated, and the health benefits were

Component	Description
	underestimated. • The cost used for a 4 mg pomalidomide capsule ($425) was higher than the cost cited in the pCPA generic categories report as well as some jurisdictions in Canada ($125). Likewise, the cost used for bortezomib ($1,402.42 per 3.5 mg) was higher than the cost used in previous CDA-AMC reviews ($654.31 per 3.5 mg). • OOS products were assumed not to be reimbursed by the public payer. There remains uncertainty as to whether OOS product costs would not be borne by public plans.
CDA-AMC reanalysis results	• We addressed key limitations with respect to model structure, extrapolation of OS, subsequent therapy costs, cost of pomalidomide and bortezomib, carfilzomib treatment schedule, and OOS product costs. Due to immature data and no long-term follow-up, extrapolation of long-term OS was uncertain. This was explored through scenario analyses. • In our reanalysis, based on a sequential analysis, cilta-cel was associated with an ICER of $280,871 per QALY gained compared to Vd (incremental cost: $639,096; incremental QALYs: 2.28). • Results from scenario analyses that used alternative extrapolations of OS led to a range of ICERs from $182,011 to $506,778 per QALY gained based on sequential analyses.

Cilta-cel = ciltacabtagene autoleucel; DVd = daratumumab-bortezomib-dexamethasone; ICER = incremental cost-effectiveness ratio; IsaKd = isatuximab-carfilzomib-dexamethasone; IsaPd = isatuximab-pomalidomide-dexamethasone; KD = carfilzomib-dexamethasone; LY = life year; MM = multiple myeloma; OOS = out of specification; OS = overall survival; pCPA= pan-Canadian Pharmaceutical Alliance; PD = pomalidomide-dexamethasone; PFS = progression-free survival; QALY = quality-adjusted life-year; SVd = selinexor-bortezomib-dexamethasone; Vd = bortezomib-dexamethasone; vs. = versus.

Budget Impact

Based on our base case, the estimated incremental budget impact of funding cilta-cel for the treatment of adult patients with MM, who have received 1 to 3 prior lines of therapy, including a proteasome inhibitor and an immunomodulatory drug, and whose disease is refractory to lenalidomide was $129,790,049 in year 1; $166,040,215 in year 2; and $180,984,153 in year 3. Therefore, the 3-year incremental budget impact was $476,814,416. Our analysis and the sponsor analysis predict a similar spend on cilta-cel (approximately $670 million). The main difference between our estimate and the 1 provided by the sponsor are the costs associated with comparator regimens. The sponsor's analysis does not accurately incorporate treatment discontinuation whereas our analysis does. However, our reanalysis does not account for subsequent therapies.

pERC Information

Members of the Committee

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Philip Blanchette, Dr. Kelvin Chan, Dr. Matthew Cheung; Dr. Michael Crump, Dr. Jennifer Fishman, Mr. Terry Hawrysh, Dr. Yoo-Joung Ko, Dr. Christian Kollmannsberger, Dr. Catherine Moltzan, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik

Meeting date: September 11, 2024

Regrets: None

Conflicts of interest: None

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Questions or requests for information about this report can be directed to Requests@CDA-AMC.ca.