Canada's Drug and
Health Technology Agency

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

Teclistamab (TECVAYLI)

Indication: For the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least 3 prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy.

Sponsor: Janssen Inc.

Recommendation: Reimburse with Conditions

Single Technology

Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that teclistamab be reimbursed for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least 3 prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One phase I/II, single-arm, open-label trial (MajesTEC-1) demonstrated that treatment with teclistamab may result in benefits in clinical response rates, overall survival (OS), and progression-free survival (PFS) for adult patients with relapsed or refractory MM (MM) who have received at least 3 prior lines of therapy, including a proteasome inhibitor, an immunomodulatory drug, and an anti-CD38 antibody. The overall response rate (ORR) was 63.0% (95% confidence interval [CI], 55.2% to 70.4%) in this heavily pre-treated population, which met the prespecified primary end point ███████████████████████, and complete response or better was 45.5% (95% CI, 37.7% to 53.4%), which were considered clinically meaningful by clinical experts. Although associated with uncertainty due to the single-arm design of the MajesTEC-1 trial, the OS and PFS results were considered promising by pERC. After a median duration of follow-up of 22.8 months, the median OS was 21.9 months (95% CI, 15.1 to NE months), and the ████████ ██████████████████. The median PFS was 11.3 months (95% CI, 8.8 to 16.4 months), and the ████████████████████████. Furthermore, despite uncertainty in the results of the indirect treatment comparisons due to methodological limitations, there was consistency in the direction of effects favouring teclistamab over real-world physician's choice therapy across the outcomes assessed, including clinical responses, OS, and PFS. Teclistamab treatment was associated with a manageable toxicity profile.

Patients identified a need for accessible and effective treatment options, beyond third line, that delay disease progression, prolong survival, improve quality of life, and have manageable side effects with ease of administration. Given the totality of the evidence, pERC concluded that teclistamab may be an effective and more accessible treatment option with manageable side effects that may delay disease progression and prolong survival. While recognizing the uncertainty in the evidence, pERC acknowledges that teclistamab could be more accessible compared to the relevant comparator CAR-T cell therapy.

Using the sponsor submitted price for teclistamab and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for teclistamab was $506,518 per quality-adjusted life-year (QALY) gained compared with treatment of physician's choice in the submitted population. At this ICER, teclistamab is not cost-effective at a $50,000 per QALY willingness-to-pay (WTP) threshold. A price reduction is required for teclistamab to be considered cost-effective at this threshold.

Table 1. Reimbursement Conditions and Reasons

	Reimbursement condition	Reason	Implementation guidance
Initiation			
1.	Teclistamab should be reimbursed in adult patients aged 18 years or older who meet all the following criteria: 1.1 documented diagnosis of MM 1.2 documented evidence of progressive disease within the previous 6 months 1.3 received at least 3 prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 antibody 1.4 refractory to their last treatment 1.5 patients must have good performance status.	In the MajesTEC-1 trial, treatment with teclistamab demonstrated a clinical benefit in adult patients with a documented diagnosis of MM who had received at least 3 prior lines of therapy including a proteasome inhibitor and an immunomodulatory agent, and received a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 antibody, had documented progressive, and an ECOG performance status of 0 or 1.	pERC acknowledged that clinicians may consider using teclistamab for patients with an ECOG performance status ≥ 2 at their discretion.
2.	Teclistamab should not be initiated in patients with active CNS involvement or exhibiting signs of meningeal involvement of MM, or plasma cell leukemia.	The MajesTEC-1 trial excluded patients with active CNS involvement or exhibiting signs of meningeal involvement of MM, or plasma cell leukemia.	—
Discontinuation			
3.	Treatment with teclistamab should be discontinued upon the occurrence of any of the following, whichever occurs first: 5.1. disease progression 5.2. unacceptable toxicity	Treatment with teclistamab in the MajesTEC-1 study was given until disease progression or unacceptable toxicity, whichever occurred first.	—
Prescribing			
4.	Teclistamab should be administered by health professionals at treatment centres with adequate medical resources and personnel to manage severe reactions, including cytokine release syndrome and neurologic toxicities.	To ensure that teclistamab is prescribed only for appropriate patients and adverse events are managed in an optimized and timely manner.	pERC recognized that access to tocilizumab for the treatment of cytokine release syndrome is necessary.
Pricing			
5.	A reduction in price	The ICER for teclistamab is $506,518 per QALY gained when compared to treatment of physician's choice (TPC). A price reduction of at least 89% would be required for teclistamab to achieve an	—

Reimbursement condition	Reason	Implementation guidance
	ICER of $50,000 per QALY compared to TPC. uncertainty remains, due to the limitations of the indirect comparative evidence, it was noted that higher price reductions may be required.	
Feasibility of adoption		
6. Feasibility of adoption of teclistamab must be addressed	At the submitted price, the incremental budget impact of teclistamab is expected to be greater than $40 million in years 2 ($57,027,919) and 3 ($92,228,347).	—

ECOG = Eastern Cooperative Oncology Group; ICER = incremental cost-effectiveness ratio; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; QALY = quality-adjusted life-year.

Discussion Points

- Considering the severity of relapsed or refractory MM in adult patients and the significant unmet need for effective treatments in the fourth-line and later setting, pERC concluded that although the available efficacy and safety evidence was from a single-arm, noncomparative phase I/II trial, based on the totality of the evidence teclistamab has the potential to reduce morbidity and mortality associated with the disease.

- pERC discussed additional supporting data for patients previously treated with BCMA-targeted therapy. The findings from this analysis were consistent with the results from the pivotal cohort in MajesTEC-1; however, only 40 patients were included, which limits interpretation of the cohort findings. While pERC acknowledged that the clinical experts expressed that patients previously treated with BCMA-targeted therapy (e.g., CAR-T cell therapy) may be eligible for treatment with teclistamab, pERC concluded that there is limited evidence to use teclistamab in patients previously treated with BCMA-targeted therapy (e.g., CAR-T cell therapy or antibody-drug conjugate, such as belantamab).

- pERC discussed that the dosage of teclistamab can be switched from weekly to every 2 weeks or monthly dosing after response criteria are met, or due to adverse events. In the MajesTEC-1 study, patients could change from weekly dosing of teclistamab to every 2 weeks or monthly dosing due to adverse events, or if the patient achieved PR or better and received a minimum of 4 cycles of therapy (Phase 1) or CR or better for a minimum of 6 months (Phase 2). pERC concluded that there is limited evidence that switching teclistamab to every 2 weeks or monthly dosing is as effective as teclistamab taken weekly.

- pERC discussed the indirect treatment comparisons (ITCs) submitted by the sponsor, including 4 ITCs using inverse probability of treatment weighting (IPTW) and 2 unanchored matching-adjusted indirect comparisons (MAICs) of teclistamab relative to real-world physician choice (RWPC) therapy, ciltacabtagene autoleucel, belantamab mafodin, and selinexor in combination with dexamethasone. pERC noted that although teclistamab was favoured over RWPC therapy for clinical responses, OS, PFS, and time to next treatment (TTNT), the comparative efficacy estimates remain uncertain due to the methodological limitations, heterogeneity in the populations and studies, and potential for residual confounding. pERC noted that indirect evidence comparing the results from MajesTEC-1 to ciltacabtagene autoleucel suggested that treatment with teclistamab was inferior to ciltacabtagene autoleucel for OS, PFS, and TTNT; however, these findings must be interpreted in the context of the methodological limitations of these studies, which likely limit these findings.

- pERC considered that results of the MajesTEC-1 study showed that treatment with teclistamab may have had clinically meaningful improvements from baseline in health-related quality of life (HRQoL). Patients and clinicians highlighted improvement in HRQoL as an important outcome and treatment goal for patients with RRMM. In the MajesTEC-1 trial, HRQoL was assessed as a secondary outcome; however, analyses of HRQoL outcomes were undertaken post hoc, which introduces a risk of bias in the selection of the reported results. In addition, the results of these measures were at risk of bias due to missing data, particularly at longer follow-up time points, as the analyses were performed in HRQoL-evaluable patients and the size of this population in MajesTEC-1 gradually decreased over time. In addition to a diminishing sample size, the patients reporting HRQoL outcomes later in the study are expected to be the healthiest among the population.

- pERC noted that uncertainties remain regarding the implementation of teclistamab and the systems needed to optimize timely access and deliverability of teclistamab in the real-world setting. Teclistamab must be administered at specialized treatment centres with the infrastructure and resources required to administer the treatment and manage adverse events. However, a limited number of centres in Canada have the expertise and resources to deliver teclistamab and other CRS and ICANS management as needed, and it is unlikely that qualified centres will be available in all jurisdictions. pERC considered that some patients may be unable to travel outside the province or country to receive therapy. pERC acknowledged the input from clinical experts that patients starting treatment with teclistamab will receive first 2 doses in the hospital, and after that can safely receive ongoing therapy in an outpatient setting on a case-by-case basis.

- pERC noted that patients expressed a need for treatments that have fewer side effects. pERC noted that the adverse events in the MajsesTEC-1 study were manageable, however access to supportive treatments for adverse events is needed (e.g., tocilizumab to treat cytokine release syndrome of any grade). No safety outcomes were included in any of the ITCs; therefore, pERC could not draw definitive conclusions about the safety of teclistamab relative to other treatments currently available.

- pERC noted that Health Canada indication for teclistamab is for the treatment of refractory or relapsed MM after receiving at least 3 prior lines of therapy. Patients are generally exposed to a PI, an IMID, and anti-CD38 monoclonal antibody in earlier lines of therapy. The clinical experts expressed that patients who are resistant or intolerant to a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 antibody should be eligible to receive teclistamab at the point that these therapies are no longer effective or appropriate regardless of what line of therapy it is in.

- pERC discussed the cost effectiveness of teclistamab versus ciltacabtagene autoleucel. It was noted that relative to teclistamab, ciltacabtagene autoleucel was associated with higher costs, but may also provide higher benefit. However, comparative effectiveness is highly uncertain based on the available evidence. Given ciltacabtagene autoleucel is currently under negotiation at pCPA and may not be displaced by teclistamab if funded, pERC noted that the cost-effectiveness of teclistamab relative to physician's choice was the more relevant comparison.

Background

Multiple Myeloma (MM) is a plasma cell cancer characterized by clonal proliferation of malignant plasma cells (B-cells) and overproduction of the abnormal immunoglobulin monoclonal protein (M-protein). In 2022, it was estimated that 4,000 Canadians were diagnosed with MM and 1,650 Canadians died from MM. The 5-year survival probability for patients with MM is estimated to be approximately 50%, and although survival rates have improved in recent years due to advances in therapeutic options, MM remains incurable. The majority of patients with MM will relapse and many patients will become refractory to commonly used therapies. The most common symptoms of MM are fatigue and bone pain, with other symptoms including kidney problems, recurrent infections, fever, and nervous system problems. Patients with relapsed or refractory MM (RRMM) often undergo multiple rounds of treatment, with the duration of remission, depth of response, progression-free survival, and overall survival decreasing with each subsequent line of therapy. There is no preferred standard of care for treatment of RRMM in the fourth line and beyond, and at this stage of the disease patients may be exposed to a proteasome inhibitor (PI), an immunomodulatory agent (IMiD), and anti-CD38 monoclonal antibody, and in some cases receiving more than 1 PI or IMiD further limiting treatment options in later lines of therapy. The clinical experts noted that treatment options at relapse include proteosome inhibitor (bortezomib, carfilzomib) containing combinations such as cyclophosphamide in combination with bortezomib and dexamethasone (CYBOR-D), carfilzomib in combination with dexamethasone with or without cyclophosphamide, or selinexor in combination with bortezomib and dexamethasone. The clinical experts and clinician groups agreed that there is an unmet need for treatments beyond the third line that prolong survival, delay disease progression, prevent disease complications, improve quality of life, and minimize side effects.

Teclistamab injection is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least 3 prior lines of therapy, including PI, IMiD, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy. Teclistamab is a bispecific antibody that targets the CD3 receptor expressed on the surface of T-cells and B-cell maturation antigen (BCMA) expressed on the surface of malignant multiple myeloma and healthy B-lineage cells and plasma cells. Teclistamab redirects CD3-positive T-cells to BCMA-expressing myeloma cells to induce killing of tumor cells. The recommended dosage for teclistamab is 1.5 mg/kg of body weight after receiving step-up doses of 0.06 mg/kg and 0.3 mg/kg of body weight. One to 3 hours prior to each teclistamab step-up dose and the first full-strength treatment dose, all subjects must receive a corticosteroid (16 mg oral [PO] or intravenous [IV] dexamethasone), an antihistamine (50 mg PO or IV diphenhydramine or equivalent), and an antipyretic (650 mg to 1,000 mg PO or IV acetaminophen or equivalent).

Sources of Information Used by the Committee

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

- a review of 1 Phase 1/2, open-label, multicenter, clinical study in patient with relapsed or refractory multiple myeloma
- patient perspectives gathered by 1 patient group: Myeloma Canada
- input from public drug plans and cancer agencies that participate in the CADTH review process
- 2 clinical specialists with expertise diagnosing and treating patients with relapsed or refractory multiple myeloma
- input from 2 clinician groups, including the Canadian Myeloma Research Group (CMRG) and Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee (OH-CCO's Drug Advisory Committees)
- a review of the pharmacoeconomic model and report submitted by the sponsor
- a review of the indirect evidence from 6 indirect treatment comparisons (ITCs) submitted by the sponsor.

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient and clinician groups who responded to CADTH's call for input and from clinical experts consulted by CADTH for the purpose of this review.

Patient Input

CADTH received 1 patient group submission from Myeloma Canada, which has existed for over 15 years to support the growing number of Canadians diagnosed with myeloma, and those living longer than ever with the disease access new and innovative therapies. Myeloma Canada gathered information for this review through a patient and caregiver (33 patients and 3 caregivers) survey that was conducted from August 28 to September 6, 2023.

Patient respondents indicated that their ability to travel was the most significantly impacted by symptoms associated with myeloma, followed by ability to work and to exercise. Patient and caregiver respondents identified the following factors as the most important to myeloma treatment: improved quality of life, manageable side effects, along with the effectiveness of treatment, especially in achieving remission and having a long and durable response, and treatment accessibility or portability (including fewer or minimal visits to the hospital or cancer centre). In terms of treatment outcomes, 13 of the 22 respondents rated improved quality of life as extremely important, 6 as very important, and 3 as somewhat important. A total of 17 of the 22 patients rated the estimated minimum of 1 year to 21 months of life extension as extremely desirable, and 5 as very desirable. All caregiver respondents felt that caring for someone with myeloma had the most impact on 'anxiety/worry', followed by 'interruption of life goals/accomplishments (career, retirement, etc.).

From August 28 to September 30, 2022, Myeloma Canada also conducted a different survey about a CAR T-cell therapy which received over 200 responses, and 11 patient respondents from this survey had experience with teclistamab. Myeloma Canada emphasized that this is indicative of the comparative ease with which teclistamab can and has been made accessible to Canadians with triple-class exposed RRMM.

Clinician Input

Input From Clinical Experts Consulted by CADTH

The clinical experts consulted by CADTH for this review highlighted that the most important goals of treatment for patients with MM are to prolong survival, delay disease progression, prevent disease complications, improve quality of life, and minimize side effects. The clinical experts noted that clinicians try not to re-use the same drugs in subsequent lines of therapy, and after receiving 3 lines of therapy, the majority of patients will be triple refractory and will need new families of drugs. The clinical experts also mentioned that beyond third line of therapy, the treatment options are getting more restricted, and some patients do not respond to the current standard therapies. Thus, there is a need for treatments for fourth-line and beyond that are tolerable for patients. The clinical experts consulted by CADTH indicated that, given that the prognosis of MM worsens as patients move on to subsequent lines of therapy, any patient with RRMM will require this intervention. The clinical experts noted that teclistamab in not the first approved treatment that targets BCMA expression on the myeloma cell; however, this drug has a novel mechanism of action that is very different from any current available therapies. The clinical experts agreed that there is no evidence that some patients are more likely to respond to treatment, and there are no disease specific characteristics that would make a patient ineligible for treatment with teclistamab. The clinical experts noted that teclistamab represents a new class of agents that can help sustain the quality of life and extend the duration of life in patient with RRMM.

The clinical experts identified overall survival, progression-free survival, and clinical response outcomes as the most important outcomes for assessing the response to treatment. The clinical experts agreed that the best possible response to treatment would be complete remission that is minimal residual disease (MRD)-negative, and less deeper responses include complete response, very good partial response, partial response, and stable disease. The clinical experts further noted that complete response and very good partial response are the most desirable outcomes in most situations, even achieving stable disease is acceptable. The clinical experts consulted by CADTH indicated that the main reason for discontinuing treatment with teclistamab would be relapse of MM. The clinical experts further noted that as with any treatment, it can be expected that some patients will be forced to discontinue treatment due to intolerable side effects. The clinical experts consulted mentioned that currently all patients receiving teclistamab are

treated at tertiary care centers and are admitted to the hospital for the first few doses. The clinical experts also noted that depending on the situation, patients starting treatment with teclistamab will require treatment at a larger hospital capable of providing management and monitoring; however, after patients receive the first few doses of this treatment, they can receive ongoing therapy at community centers and smaller cancer centers.

Clinician Group Input

The clinician group input was obtained from 2 clinician groups, including the Canadian Myeloma Research Group (CMRG) and Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee (OH-CCO's Drug Advisory Committees). CMRG gathered information through teleconferences with physicians, and OH-CCO Drug Advisory Committees gathered information through videoconferencing and email communications.

Both CMRD and OH-CCO's Drug Advisory Committees mentioned that myeloma remains incurable, and patients eventually become refractory to all available funded agents. One major unmet need mentioned by clinician groups is that patients with advanced disease who have received multiple lines of treatment and have already received the 3 major drugs (triple-class exposed or refractory), including an IMID, PI and anti-CD38 monoclonal antibody have no other substantial treatment other than CAR-T therapy. CMRG also emphasized that the clinical features associated with advanced disease and short duration of responses lead to a poor quality of life, significant caregiver burden, and a shortened patient lifespan. Thus, this situation also represents 1 of the most pressing unmet needs in Canada for patients with MM. Another unmet need noted by OH-CCO Drug Advisory Committees is to achieve ease of administration (i.e., subcutaneous injection and no need for apheresis).

Both clinician groups agreed that teclistamab is another option for triple-class exposed patients. They believe that currently, it would be used in sequence after other lines of therapy for myeloma, i.e., after failure of multiple agents, it is not expected to impact the sequencing of agents earlier in the disease course or lead to a major change in treatment algorithms prior to patients becoming triple-class exposed or refractory.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process.

The clinical expert consulted by CADTH provided advice on the potential implementation issues raised by the drug programs. Refer to Table 2 for details.

Table 2: Responses to Questions from the Drug Programs

Drug program implementation questions	pERC response
Relevant comparators	
How does teclistamab compare to currently funded options in this therapeutic space (i.e., pomalidomide plus dexamethasone with or without cyclophosphamide and carfilzomib plus dexamethasone with or without cyclophosphamide)? Selinexor with bortezomib and dexamethasone is funded in some jurisdictions as 4th line therapy (and beyond) for patients sensitive to bortezomib but not anti-CD38 and lenalidomide.	pERC agreed with clinical experts that teclistamab in MajesTEC-1 study has better progression-free survival when indirectly compared with that of pomalidomide in combination dexamethasone with or without cyclophosphamide, or carfilzomib in combination with dexamethasone with or without cyclophosphamide. However, teclistamab would be used when patients with RRMM have received pomalidomide or carfilzomib, or both.
Cilta-cel is also used in this setting; however, it is under consideration for negotiation. The CADTH reimbursement conditions for cilta-cel specified that it should not be reimbursed in patients who have received prior treatment with therapy targeting BCMA.	No response required. For pERC consideration.
Considerations for initiation of therapy	
Should patients previously treated with BCMA-targeted therapy (e.g., cilta-cel) be eligible for teclistamab? Is there evidence to support this sequence? Should patients treated with teclistamab be eligible for CAR-T cell therapy (e.g., cilta-cel)? Is there evidence to support this sequence?	pERC acknowledged that clinical experts expressed that it is reasonable that patients previously treated with BCMA-targeted therapy (e.g., CAR-T cell therapy) would be eligible for teclistamab; however, there is limited evidence to support this.
The Health Canada approval is for patients who have had at least 3 prior lines of therapy, including a proteosome inhibitor, an immunomodulatory agent, and an anti-CD38. Patients who could not tolerate a PI, IMid, or anti-CD38 were allowed per the MajesTEC-1 trial. Are 3 prior lines of therapy required if a patient is resistant to a proteasome inhibitor, immunomodulatory agent and anti-CD38 antibody (e.g., received all 3 classes of these drugs, but across 2 lines of therapy)?	There is no evidence reviewed to inform this. pERC acknowledged the clinical experts' opinion that patients who are resistant to PIs, an immunomodulatory agent, and an anti-CD38 antibody (i.e., all 3), or intolerant to any of them and resistant to the others should be eligible to receive teclistamab, regardless of what line of therapy it is in.
Considerations for discontinuation of therapy	
Patients with prolonged treatment interruptions may require re-administration of step-up dosing.	No response required. For pERC consideration.
Considerations for prescribing of therapy	
Teclistamab must be administered according to a step-up dosing schedule: • 0.06mg/kg SC on Day 1 (step up dose 1) • 0.3mg/kg SC on Day 3 (step up dose 2; may be given 2 to 7 days after step up dose 1), • 1.5mg/kg SC on day 5 (first treatment dose; may be given 2 to 7 days after step up dose 2) • followed by 1.5 mg/kg SC weekly beginning 1 week after first treatment dose.	pERC acknowledged that clinical experts noted that switching from weekly to every 2 weeks dosing should occur primarily due to side effects, toxicity, or patient choice. The clinical experts also noted that in clinical practice, physicians typically switch to less frequent dosing once the patient has responded to treatment. However, pERC concluded that there is limited evidence that teclistamab, when switched to every 2 weeks dosing, is as effective as weekly dosing.

Drug program implementation questions	pERC response
The 10 mg/mL vial is used for step up dose 1 and step up dose 2 while 90mg/mL is used for remaining doses. The trial protocol allowed patients to be switched to a every 2 weeks dosing schedule (1.5 mg/kg SC every 2 weeks) if they achieved a complete response or greater for a minimum of six months. Can pERC clarify the dosing schedule for teclistamab, including when every 2 weeks dosing would be appropriate?	
Cytokine release syndrome and ICANS can occur with teclistamab, although the severity and incidence appeared to be low in the trial. Tocilizumab may be needed to treat cytokine release syndrome. Can teclistamab be safely administered in the outpatient setting?	pERC acknowledged that the clinical experts noted that patients starting treatment with teclistamab will receive first 2 doses in the hospital, and after that they can safely receive ongoing therapy in an outpatient setting on a case-by-case basis. pERC highlighted that hospitalization may likely be needed for patients who have CRS requiring tocilizumab.
The product monograph recommends that patients remain within proximity of a healthcare facility and monitor daily for 48 hours for signs and symptoms of CRS after administration of all doses within the teclistamab step-up dosing schedule, or alternatively consider hospitalization for patients. Patients who experience greater than grade 1 CRS should be monitored daily for 48 hours following the next dose of teclistamab and remain within proximity of a healthcare facility. Jurisdictions may encounter capacity issues due to supportive care requirements.	No response required. For pERC consideration.
Generalizability	
Should teclistamab be used in the following patients? • with ECOG performance status greater than 1 • with CNS disease that is under treatment or controlled • with plasma cell leukemia or amyloidosis	pERC acknowledged that the clinical experts expressed that teclistamab can be used in patients with MM with ECOG performance status greater than 1, in patients with amyloidosis as a complication of MM , and in patients with CNS disease that is under treatment or controlled, although this is rare. The clinical experts also noted that teclistamab can be used in patients with plasma cell leukemia at usual doses; however, these patients in general are excluded from the trials because their disease is more aggressive.
At the time of funding, should patients receiving alternative therapies (i.e., Pd or Kd with or without cyclophosphamide) be eligible to switch to teclistamab?	pERC agreed with clinical experts that physicians usually would not switch effective treatments until they no longer work; however, it can be switched to another drug if it stops working.
Funding algorithm	
Complex therapeutic space with multiple lines of therapy, subpopulations, or competing products	No response required. For pERC consideration.

Drug program implementation questions	pERC response
There may be interest in sequencing teclistamab with other BCMA-targeted agents.	No response required. For pERC consideration.
Care provision issues	
Teclisimab is supplied as 153mg/1.7mL (90mg/mL) and 30mg/3mL (10mg/mL) However, drug wastage would be incurred due to the step-up and mg/kg dosing. There is a risk of medication error with 2 different concentrations. The drug may need to be initiated in the inpatient setting, in which case, the drug cost would be outside of the drug program budget in some provinces.	No response required. For pERC consideration.
System and economic issues	
There is concern about feasibility of adoption (budget impact) in light of the cost of prior therapies and potential for subsequent therapies.	No response required. For pERC consideration.
Generic pomalidomide is available, and confidential pricing exists for carfilzomib.	No response required. For pERC consideration.

BCMA = B cell maturation antigen; CAR-T = chimeric antigen receptor; cilta-cel = ciltacabtagene autoleucel; CNS = central nervous system; CRS = Cytokine Release Syndrome; ECOG = Eastern Cooperative Oncology Group; ICANS = immune effector cell-associated neurotoxicity syndrome, Kd = carfilzomib in combination with dexamethasone; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; Pd = pomalidomide in combination with dexamethasone; Q2W = twice a week; Q4W = monthly; SC = subcutaneous.

Clinical Evidence

Systematic Review

Description of Studies

MajesTEC-1 (n = 165) is a phase 1/2, open-label, multicenter study assessing the efficacy and safety of teclistamab administered to adult patients with RRMM. The study is still ongoing and being conducted in 39 sites across 10 countries, including Canadian patients who were enrolled at 4 Canadian sites. The MajesTEC-1 study was conducted in 3 parts, including Part 1 or dose escalation (Phase 1), Part 2 or dose expansion (Phase 1) at a proposed recommended phase 2 dose (1.5 mg/kg subcutaneously weekly), and Part 3 or dose expansion (Phase 2) in cohorts of patients with RRMM with unmet medical need (Phase 2). The primary objectives reported in Phase 1 of MajesTEC-1 were to: 1) identify the proposed recommended phase 2 dose and dose schedule assessed to be safe in Part 1, and 2) characterize the safety and tolerability of teclistamab at the proposed recommended phase 2 dose in Part 2. The primary objective Phase 2 of MajesTEC-1 was to evaluate the efficacy and safety of teclistamab at the proposed recommended phase 2 dose. In Phase 2 of the MajesTEC-1 study, Cohort A enrolled patients with RRMM who have received at least 3 prior lines of therapy that included a PI, an IMiD, an anti-CD38 monoclonal antibody, while Cohort C enrolled patients who have received at least 3 prior lines of therapy that included a proteasome inhibitor (PI), an immunomodulatory drug (IMiD), an anti-CD38 monoclonal antibody, and an anti-BCMA treatment (CAR-T cells or an antibody-drug conjugate [ADC]). The primary efficacy outcome for MajesTEC-1 was overall response rate (ORR), the secondary efficacy outcomes included very good partial response (VGPR) or better, complete response (CR) or better, stringent complete response (sCR), time to response (TTR), duration of response, overall survival (OS), progression-free survival (PFS), minimal residual disease (MRD)-negativity rate, and patient-reported outcomes. Time to next treatment (TTNT) was an exploratory outcome in Phase 2 of the MajesTEC-1 study. Disease

responses were evaluated by the independent research committee (IRC) using International Myeloma Working Group (IMWG) 2016 criteria in both Phase 1 and Phase 2 Cohort A.

In MajesTEC-1, the median age of the patients was 64.0 years (range: 33.0 to 84.0 years), with ███████████████████████████. Ninety-six patients (58.2%) were male, and 69 patients (41.8%) were female. Most patients were white (81.2%), and 12.7% identified as Black. Most patients had an Eastern Cooperative Oncology Group (ECOG) score of 1 (66.1%), and 33.3% of patients had an ECOG score of 0. ██████████████████████ ████████████. The median time from diagnosis of MM to enrollment in the study was 6.0 years (range: 0.8 to 22.7 years). Twenty-eight patients (17.0%) had 1 or more extramedullary plasmacytomas at baseline. Of the 147 patients with baseline cytogenetic data reported, 38 patients (25.9%) had at least 1 high-risk abnormality, including del(17p) (15.6%) and t(4;14) (10.9%) abnormality. Of the 162 patients with baseline International Staging System (ISS) data reported, 85 patients (52.5%) were ISS Stage I, 57 patients (35.2%) were ISS Stage II, while 20 patients (12.3%) were ISS Stage III.

Efficacy Results

The primary analysis at the clinical cut-off date of September 2021 and the final analysis at the clinical cut-off date of August 2023 were prespecified analyses, and the Clinical Study Reports submitted by the sponsor with clinical cut-offs of March 2022 and January 2023 were interim analyses. As the final report for the pivotal study is not yet available, information for the following sections was extracted from the more recent Clinical Study Report with a clinical cut-off date of January 4, 2023 submitted by the sponsor for this review. However, data from the clinical cut-off date of September 7, 2021 was also used to supplement the included data when necessary.

Overall Survival

At the time of analysis, using the January 4, 2023 data cut-off, the median duration of follow-up was 22.8 months (range: 0.3 to 33.6 months). The estimated median OS was 21.9 months (95% confidence interval [CI], 15.1 to NE months). In the Full Analysis Set (FAS), deaths were reported in ████████ in Phase 1 and ████████ in Phase 2 Cohort A of MajesTEC-1. The 9 months OS probability was ███████████████ the 12 months OS probability was ██████████████ and the 24 months OS probability was ████ ████████.

Progression-free Survival

At the time of analysis, using the January 4, 2023 data cut-off, the estimated median PFS was 11.3 months (95% CI, 8.8 to 16.4 months) in MajesTEC-1. In the FAS, the 9 months PFS probability was ███████████████ the 12 months PFS probability was ████ ██████████ and the 24 months PFS probability was ██████████████.

CR or better

At the time of analysis, using the January 4, 2023 data cut-off, ███████████████████ in Phase 1 and ███████████████████ achieved CR or better (CR, or sCR).

sCR

██

MRD-negativity status

Updated data regarding the MRD-negativity rate based on the January 4, 2023 clinical cut-off date are not available.

At the time of the data cut-off date of September 7, 2021, 37 patients (24.7%, [95% CI, 18.0 to 32.4]) achieved MRD negativity at 10^{-5} bone marrow cells. Among 43 patients who achieved CR or better, 18 patients (41.9%, [95% CI, 27.0% to 57.9%]) achieved MRD negativity at 10^{-5} bone marrow cells.

VGPR or better

At the time of analysis, using the January 4, 2023 data cut-off, ████████████████████ in Phase 1 and ████████████ achieved VGPR or better (VGPR, CR, or sCR).

ORR

At the time of analysis, using the January 4, 2023 data cut-off, 104 patients (63.0%) (95% CI, 55.2% to 70.4%) achieved an overall response (PR or better), and ORR was similar across patients treated in Phase 1 and Phase 2 Cohort A (████████████████ ████████████████████). Of the 104 responders (who achieved PR or better), 51 patients (49.0%) maintained their response until the clinical cut-off date ████████████████████ including 46 patients (44.2%) who were still on treatment. Of the 104 responders, █ ████████ had disease progression after initial response, of which ████████ died after disease progression, ████████ discontinued the study treatment, and ████████ remain on study treatment. A total of ████████ died after achieving response and without experiencing disease progression, and ████████ had subsequent therapy after response and without progressive disease. Of the 63 respondents who changed their dosing schedule from weekly to every 2 weeks or monthly dosing, 42 patients (66.7%) maintained their response until the clinical cut-off date of January 4, 2023, including 41 patients (65.1%) who remain on treatment.

Subgroup analysis

Only results of the ORR subgroup analyses that were deemed clinically meaningful by the clinical experts consulted by CADTH for this review are reported. At the time of analysis, using the January 4, 2023 data cut-off, 32 patients (74.4%) of 43 patients who received 3 or less prior lines of therapy achieved an overall response. Of the 122 patients who received more than 3 prior lines of therapy, 72 patients (59.0%) achieved overall response, and 32 patients of 60 patients (53.3%) with high cytogenetic risk and/or extramedullary disease achieved overall response.

Time to Response

At the time of analysis, using the January 4, 2023 data cut-off, in 104 responders, the median time to first response was 1.18 months (range: 0.2 to 5.5 months), while the median time to best response was 3.96 months (range: 1.1 to 18.7 months). Most patients demonstrated their first response rapidly, by the start of Cycle 2 of the MajesTEC-1 study.

Duration of Response

At the time of analysis, using the January 4, 2023 data cut-off, the median duration of response was 21.6 months (95% CI, 16.2 to NE months) in MajesTEC-1. Among 104 responders, ████████ in Phase 1 and ████████ in Phase 2 Cohort A had disease progression or died due to any cause. The probability of patients remaining in response at 9 months was ████████████████ The probability of patients remaining in response at 18 months was ████████████████ The probability of patients remaining in response at 24 months was ████████████████

Patient-reported Outcomes

Patient-reported outcomes (PRO) were assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 Item (EORTC-QLQ-C30) assessment, the EuroQol Five Dimension Five Level (EQ-5D-5L) Questionnaire, and the Patient Global Impression of Severity (PGIS) scale. The HRQoL results were reported only for Phase 2 Cohort A of the MajesTEC-1 study. Analyses were conducted in the HRQoL-evaluable population of patients who had evaluable assessment at baseline and follow-up time points for each domain of EORTC-QLQ-C30 (i.e., Cycle 2 Day 1, Cycle 3 Day 1, etc.).

EORTC-QLQ-C30

At the time of analysis, using the January 4, 2023 data cut-off, the results of a post hoc analysis of the EORTC QLQ-C30 showed

███

At the time of analysis, using the September 7, 2021 data cut-off, meaningful improvement from baseline (10 points using the literature-based meaningful change threshold [MCT]) to Cycles 2, 4, and 6 was reported by up to 35.8% of patients for Global Health Status, up to 23.9% of patients for Physical Functioning, up to 68.7% of subjects for Fatigue System scale, and up to 78.8% of patients for Pain.

EQ-5D-5L

At the time of analysis, using the January 4, 2023 data cut-off, the results of a post hoc analysis of the EQ-5D-5L showed ████████ ██

At the time of analysis, using the September 7, 2021 data cut-off, meaningful improvement from baseline (7 points using the literature-based MCT in VAS scores at Cycles 2, 4, and 6 was reported by 23.8%, 28.6%, and 30.2% of patients, respectively. By Cycle 8, 50% of patients reported meaningful improvement in the VAS score.

Time to next treatment

Time to next treatment was an exploratory end point in Phase 2 Cohort A of the MajesTEC-1 study, and it was not reported in the CSR at the clinical data cut-off date of January 4, 2023.

At the time of analysis, using the September 7, 2021 data cut-off, subsequent anti-myeloma therapy and/or death due to progressive disease was reported for ████████ with a median time to next treatment of ████████████

Harms Results

At the time of analysis, using the January 4, 2023 data cut-off, patients in the MajesTEC-1 study experienced at least 1 treatment-emergent adverse event (TEAE). The most common TEAEs occurring in at least 25% of patients in either phase of the study were CRS (72.1%), neutropenia (71.5%), anemia (54.5%), thrombocytopenia (42.4%), lymphopenia (36.4%), diarrhea (33.9%), and pyrexia (31.5%). In MajesTEC-1, ████████ experienced TEAEs of Common Terminology Criteria for Adverse Events (CTCAE) Grade 3, ████████ experienced TEAEs of Grade 4, and ████████ experienced TEAEs of Grade 5. The most common TEAEs of Grade 3 or 4 were neutropenia (65.5%), anaemia (37.6%), lymphopenia (34.5%), and thrombocytopenia (22.4%). The most common TEAEs of Grade 5 were COVID-19 (10.8%), and general physical health deterioration (2.4%). At the time of analysis, using the January 4, 2023 data cut-off, 113 patients (68.5%) experienced at least 1 serious TEAE in MajesTEC-1. The most common serious TEAEs occurring in at least 5% of patients in either phase of the study were pneumonia (20.6%), CRS (10.9%), pyrexia (8.5%), acute kidney injury (5.5%), and general physical health deterioration (5.5%). At the time of analysis, using the January 4, 2023 data cut-off, ████████ stopped study treatment due to TEAEs in MajesTEC-1. The most common reasons for stopping study treatment included ██ A total of ████████ died during the study, ████████████ who died due to TEAEs.

In the MajesTEC-1 study, several adverse events of clinical interest were identified, including CRS, neurological adverse events (AEs) and neurotoxicity, immune effector cell-associated neurotoxicity syndrome (ICANS), systemic administration-related reactions, injection-site reactions, hypogammaglobinemia, cytopenia, and infections. At the time of analysis, using the January 4, 2023 data cut-off, 119 patients (72.1%) experienced CRS events, of which 83 patients (50.3%) experienced Grade 1 events, and 35 patients (21.2%) experienced Grade 2 events. One patient (0.6%) experienced CRS events of Grade 3, and no patients experienced CRS events of Grade 4 or Grade 5. ██ ██. In MajesTEC-1, a total of 132 patients (80.0%) had infections of any Grade. The most common infections and infestations included ████████████████ ██ In MajesTEC-1, 71 patients (43.0%) experienced at least 1 infection and infestation of Grade 3 or 4, while 21 patients (12.7%) experienced at least 1 infection and infestation of Grade 5. At the time of analysis, using the January 4, 2023 data cut-off, ████████ experienced at least 1 hypogammaglobulinaemia TEAE, including ████████ with a case of hypogammaglobulinaemia, and ████████ with a case of hypoglobulinaemia. A total of 152 patients (92.1%) experienced at least 1 treatment-emergent cytopenic event, including neutropenia (71.5%), aneamia (55.8%), thrombocytopenia (42.4%), and lymphopenia (36.4%). A total of 108 patients (65.5%) experienced treatment-emergent neutropenia of Grade 3 or greater, 62 patients (37.6%) experienced anemia of Grade 3 or greater, 37 patients (22.4%) experienced thrombocytopenia of Grade 3 or greater, and 57 patients (34.5%) experienced lymphopenia of Grade 3 or greater. A total of 61 patients (37.0%) experienced at least 1 case of injection site reaction events, including 32.1% cases of Grade 1, and 4.8% cases of Grade 2.

Critical Appraisal

MajesTEC-1 was a multicentre, single-arm, open-label, phase 1/2 study. Due to the lack of a comparator arm, the benefit of teclistamab compared to placebo or reference treatment was not documented. A single-arm study design is usually used when the purpose of the study is to provide preliminary evidence of the efficacy of a treatment and to collect additional safety data and not intended to be confirmatory for efficacy. Thus, a single-arm study design is a subject of several limitations that complicate the interpretation of the study results. An open-label design of the MajesTEC-1 study may increase uncertainty in subjective outcomes, including clinical response outcomes, PFS, HRQoL, and safety outcomes, introducing bias due to inherent subjectivity of the outcome in an unblinded assessor. This bias would be less likely in more objective outcomes, such as OS, if assessed against a pre-determined hypothesis. According to the Food and Drug Administration (FDA), the ORR can be evaluated in a single-arm study as a direct measure of a drug antitumor activity if it is defined as the sum of partial responses plus complete responses. In MajesTEC-1, the estimated ORR was tested against a pre-determined hypothesis of an ORR greater than 45% (with a lower bound of the ORR 2-sided 95% CI above 30%). ORR achieved the predetermined threshold for a positive outcome in MajesTEC-1. However, for ORR, there was no adjustment for multiplicity across the various analyses of the outcome (i.e., the various data cut-offs), which may have increased risk of false positive conclusions. Additionally, this report presents interim analysis results because a prespecified final analysis was not available; therefore, there is the potential that the benefit of teclistamab is overestimated; however, the presence and extent of any overestimation is uncertain.

Disease responses were evaluated by the IRC using IMWG 2016 criteria in both Phase 1 and Phase 2 Cohort A. The time-to-event end points, including OS and PFS, were identified as important outcomes by clinical experts, patient and clinician groups consulted by CADTH for this review. However, OS and PFS were not adjusted for multiplicity in MajesTEC-1, and the lack of a comparator group limits the estimation of relative effects of treatment with teclistamab. In addition, the longer-term efficacy of teclistamab for OS and PFS is unknown as the MajesTEC-1 study is ongoing. The clinical experts, patient and clinician groups consulted by CADTH for this review highlighted improvement in HRQoL as an important outcome and treatment goal for patients with RRMM. The analyses of HRQoL outcomes were undertaken post hoc, which introduces a risk of bias in the selection of the reported results. In addition, analyses for HRQoL were performed in HRQoL-evaluable patients and only for Phase 2 Cohort A rather than in the ITT population of MajesTEC-1, which may have biased the results; however, the extent of the bias with respect to the direction and magnitude of effect is uncertain. The size of the HRQoL-evaluable population in MajesTEC-1 gradually decreased over time, and the rate of missing data was high among those who remained in the study at longer follow-up visits. Therefore, data from later time points should be interpreted with caution due to the possibility that HRQoL scores could be overestimated if patients with better HRQoL were more likely to complete the questionnaires.

According to the clinical experts, the patient population in the MajesTEC-1 study generally reflects patients in clinical practice in this setting. To be enrolled in the MajesTEC-1 study, patients with RRMM were required to have ECOG performance status of 0 or 1 and have a measurable disease. The clinical experts consulted noted that this would not be reflective of clinical practice and that clinicians would prescribe teclistamab to patients with ECOG performance status of 2 or 3 and to patients without biochemically measurable disease. Patients who had previously received antitumor therapy, such monoclonal antibody, or cytotoxic therapy within 21 days before the first dose of teclistamab were excluded from the study, which the clinical experts found concerning as a washout period of 21 days is less relevant in this population. One of the exclusion criteria of pivotal MajesTEC-1 study was any prior BCMA-targeted therapy. Additional supporting data were presented for Phase 2 Cohort C at the time of clinical cut-off date of March 16, 2022, to address the use of teclistamab in patients previously treated with BCMA-targeted therapy in accordance with the Health Canada indication for teclistamab. Findings from the Phase 2 Cohort C of the MajesTEC-1 study were consistent with the results from the pivotal cohort (Phase 1 and Phase 2 Cohort A); however, only 40 patients were included, which limits interpretation of the cohort findings. According to the clinical experts consulted by CADTH, the demographic and disease characteristics of the MajesTEC-1 study population were reflective of patients lining in Canada with RRMM. The mean age of patients in MajesTEC-1 was 64 years, with clinical experts noting that in the real world setting, the mean age of patients with relapsed disease receiving fourth-line therapy and beyond would be around 70 years. About 26% of patients in MajesTEC-1 had at least 1 high-risk abnormality, including del(17p) and t(4;14), although clinical experts noted that the proportion of patients with cytogenetic risk is slightly higher in clinical practice. In the MajesTEC-1 study, 63 patients (38.2%) switched from weekly to every 2 weeks dosing of teclistamab, including 54 patients who met the response criteria, and 9 patients had switched from every 2 weeks to monthly dosing. Clinical experts consulted by CADTH believed that there would be more patients in clinical practice switching to less frequent dosing of

teclistamab. According to the clinical experts consulted by CADTH, patient and clinician groups input, OS, PFS, clinical response outcomes, and HRQoL are the most important outcomes for assessing the response to treatment. However, due to a study design, MajesTEC-1 provides no information about the efficacy and harms of teclistamab relative to treatments that would otherwise be used in this patient population in clinical practice. In MajesTEC-1, the study population was drawn from a number of sites around the globe, including Canada. The clinical experts indicated that there are no major concerns with generalizing the findings from the pivotal study to the Canadian clinical setting.

GRADE Summary of Findings and Certainty of the Evidence

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. Table 3 presents the GRADE summary of findings for teclistamab in patients with RRMM in the MajesTEC-1 study.

Table 3: Summary of Findings for Teclistamab for Patients with Refractory or Relapsed Multiple Myeloma

Outcome and follow-up	Patients (study), N	Effect	Certainty	What happens
Overall survival				
OS, months Median follow-up: 22.8 months	165 (1 single-arm trial: Phase 1 and Phase 2 Cohort A)	Median (range) duration of OS of 21.9 (15.1 to NE)	Very low[a,b]	The evidence is very uncertain about the effect of teclistamab on OS when compared with any comparator.
PFS				
PFS, months Median follow-up: 22.8 months	165 (1 single-arm trial: Phase 1 and Phase 2 Cohort A)	Median (range) duration of PFS of 11.3 (8.8 to 16.4)	Very low[a,b]	The evidence is very uncertain about the effect of teclistamab on PFS when compared with any comparator.
CR or better (CR, or sCR)				
Proportion of patients who achieved CR or better (95% CI) Median follow-up: 22.8 months	165 (1 single-arm trial: Phase 1 and Phase 2 Cohort A)	455 per 1,000 (377 to 534 per 1,000)	Very low[a,b]	The evidence is very uncertain about the effect of teclistamab on CR or better when compared with any comparator.
VGPR or better (VPGR, CR, or sCR)				
Proportion of patients who achieved VGPR or better (95% CI) Median follow-up: 22.8 months	165 (1 single-arm trial: Phase 1 and Phase 2 Cohort A)	594 per 1,000 (515 to 670 per 1,000)	Very low[a,b]	The evidence is very uncertain about the effect of teclistamab on VGPR or better when compared with any comparator.
ORR (PR, VPGR, CR, or sCR)				
Proportion of patients who achieved overall response (95% CI) Median follow-up: 22.8 months	165 (1 single-arm trial: Phase 1 and Phase 2 Cohort A)	630 per 1,000 (552 to 704 per 1,000)	Very low[a,b]	The evidence is very uncertain about the effect of teclistamab on ORR when compared with any comparator.
Duration of response				

Outcome and follow-up	Patients (study), N	Effect	Certainty	What happens
Duration of response (PR or better), months Median follow-up: 22.8 months	165 (1 single-arm trial: Phase 1 and Phase 2 Cohort A)	Median (range) duration of response of 21.6 (16.2 to NE)	Very low[a,b]	The evidence is very uncertain about the effect of teclistamab on duration of response when compared with any comparator.
Harms				
Proportion of patients with hypogammaglobulinemia Median follow-up: 22.8 months	165 (1 single-arm trial: Phase 1 and Phase 2 Cohort A)	212 per 1,000	Very low[a,b]	The evidence is very uncertain about the effect of teclistamab on hypogammaglobulinemia when compared with any comparator.
Proportion of patients with infections Median follow-up: 22.8 months	165 (1 single-arm trial: Phase 1 and Phase 2 Cohort A)	800 per 1,000	Very low[a,b]	The evidence is very uncertain about the effect of teclistamab on infections when compared with any comparator.

AE = adverse event; ALT = alanine transaminase; AST = aspartate aminotransferase; BICR = blinded independent central review; CI = confidence interval; CR = complete response; DOR = duration of response; HRQoL = health-related quality of life; NA = not applicable; NR = not reported; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumours; SAE = serious adverse event; + = censored observation.

[a] In absence of a comparator arm, conclusions about efficacy relative to any comparator cannot be drawn and certainty of evidence started at very low.

[b] −1 level for serious study limitations. Reported result is from an interim analysis, effect may be overestimated. Risk of selection bias; not clear whether patients were enrolled consecutively.

Additional Supporting Data

In MajesTEC-1, efficacy and safety results for Phase 2 Cohort C were presented to support the results of the pivotal study in accordance with the Health Canada indication for teclistamab, and to address the question from the Provincial Advisory Group regarding the use of teclistamab in patients previously treated with BCMA-targeted therapy. Phase 2 Cohort C enrolled patients with RRMM who had received 3 or more prior lines of therapy, including a PI, an IMiD, an anti-38 monoclonal antibody, and a BCMA-targeted treatment (e.g., CAR-T therapy or antibody-drug conjugate). At the time of analysis, using the March 16, 2022 data cut-off, 40 patients received at least 1 dose of teclistamab in Phase 2 Cohort C and were included in the Full Analysis Set.

At the time of analysis, using the September 7, 2021 data cut-off, 38 patients were enrolled in Phase 2 Cohort C, including 22 patients (57.9%) who were still on treatment. Baseline characteristics for these 38 patients are summarized below, since those of the 40 patients enrolled by March 16, 2022 were not reported in the Clinical Study Report. The median age of the patients was 63.5 years (range: 32 to 82 years). A total of 24 patients (63.2%) were male, and 14 patients (41.8%) were female. Most patients (89.5%) were white, and 7.9% identified as Black. All patients were triple-class exposed and a majority were penta-exposed (78.9%). The most common immunoglobulin isotypes were IgG, presenting in 18 patients (47.4%). The median time from diagnosis of MM to enrollment in the Phase 2 Cohort C was 6.5 years (range: 1.1 to 24.1 years). Eleven patients (28.9%) had at least 1 extramedullary plasmacytoma at baseline. Of the 34 patients with baseline cytogenetic data reported, 11 patients (32.4%) had at least one high-risk abnormality, most commonly del(17p). A total of 20 patients (52.6%) were ISS Stage I, while 9 patients (23.7%) were ISS Stage III. Prior anti-BCMA therapy included an antibody-drug conjugate (ADC) in 71.1% of patients, and chimeric antigen receptor (CAR) T cell therapy in 39.5% of patients.

Efficacy

At the time of analysis, using the March 16, 2022 data cut-off, the estimated median OS was 13.2 months (95% CI, 8.3 to NE months). The median duration of follow-up of 12.5 months (range: 0.7 to 14.4 months). In Phase 2 Cohort C, deaths were reported in

17 patients (42.5%) in FAS, and the proportion of patients who were censored (alive at time of data cut-off) was 23 (57.5%). The estimated 6 months OS probability among patients was ▮▮▮▮▮▮▮▮▮ the 9 months OS probability was ▮▮▮▮▮▮▮▮▮ and the 24 months OS probability was ▮▮▮▮▮▮▮▮▮

In Phase 2 Cohort C, the estimated median PFS was ▮▮▮▮▮▮▮▮▮ By the data cut-off date, a total of 24 patients (60.0%) had a PFS event, and ▮▮▮▮▮ were censored. The estimated 6 months PFS probability among patients in Phase 2 Cohort C was ▮▮▮▮▮▮▮▮ The 9 months PFS probability was ▮▮▮▮▮▮▮▮ the 24 months PFS probability was ▮▮▮▮▮▮▮

At the time of analysis, using the March 16, 2022 data cut-off, 11 patients (27.5%, [95% CI, 14.6% to 43.9%]) in Phase 2 Cohort C achieved CR or better (CR, or sCR), 11 patients (27.5, [95% CI, 14.6% to 43.9%]) achieved sCR, 19 patients (47.5%, [95% CI, 31.5% to 63.9%]) achieved VGPR or better (VGPR, CR, or sCR), and 21 patients (52.5%, [95% CI, 36.1% to 68.5%]) achieved an overall response (PR or better). At the time of analysis, using the March 16, 2022 data cut-off, of the 21 patients who achieved PR or better, the median time to first response was 1.2 months (range: 0.2 to 4.9 months), while the median time to best response was 2.9 months (range: 11.1 to 9.5 months). At the time of analysis, using the March 16, 2022 data cut-off, the estimated median duration of response was not reached in Phase 2 Cohort C. Among 21 responders (with a PR or better response), 15 patients (23.8%) had disease progression or died due to any cause. The estimated probability of patients remaining in response at 9 months ▮▮▮▮▮▮▮ ▮▮▮▮▮▮ while the probability of patients remaining in response at 12 months was 63.5% ▮▮▮▮▮▮▮▮

Harms

At the time of analysis, using the March 16, 2022 data cut-off, all patients in Phase 2 Cohort C of the MajesTEC-1 study experienced at least 1 TEAE. The most common TEAEs of any Grade occurring in at least 20% of patients in Phase 2 Cohort C were CRS (67.5%), neutropenia (65.0%), anemia (50.0%), thrombocytopenia (45.0%), lymphopenia (45.0%), constipation (35.0), diarrhea (35.0%), pyrexia (32.5%), injection site erythema (32.5%), and arthralgia (25.0%). In Phase 2 Cohort C, 9 patients (22.5%) experienced TEAEs of Grade 3, 20 patients (50.0%) experienced TEAEs of Grade 4, and 8 patients (20.0%) experienced TEAEs of CTCAE Grade 5. The most common TEAEs of Grade 3 or 4 were neutropenia (62.5%), lymphopenia (42.5%), anaemia (35.0%), and thrombocytopenia (30.0%). At the time of analysis, using the March 16, 2022 data cut-off, 24 patients (60.0%) experienced at least 1 serious TEAE. The most common TEAEs were COVID-19 (10.0%), CRS and febrile neutropenia (7.5%), and aneamia (5.0%). At the time of analysis, using the March 16, 2022 data cut-off, no patients experienced a TEAE leading to treatment discontinuation. A total of 17 patients (42.5%) had died, of which 8 patients (20.0%) died within 30 days of the last dose of teclistamab. In Phase 2 Cohort C of the MajesTEC-1 study, several AEs of clinical interest were identified, including CRS, neurological adverse events, and neurotoxicity, ICANS, injection-site reactions, hypogammaglobinemia, cytopenia, infections, and tumor lysis syndrome. At the time of analysis, using the March 16, 2022 data cut-off, 26 patients (65.0%) in Phase 2 Cohort C experienced 44 CRS events of any Grade. A total of 21 patients (52.5%) in Phase 2 Cohort C experienced at least 1 neurological TEAE. The most common neurologic TEAEs included headache (22.5%), ICANS and insomnia (10.0%), encephalopathy (5.0%), peripheral sensory neuropathy (7.5%), dizziness (5.0%), and motor disfunction (5.0%). At the time of analysis, using the March 16, 2022 data cut-off, a total of 10 patients (25.0%) experienced at least 1 neurotoxicity event, including headache (12.5%), and ICANS (10.0%). A total of 26 patients (65.0%) in Phase 2 Cohort C had at least 1 treatment-emergent infection of any Grade. The most common infections and infestations included COVID-19 (12.5%), pneumonia (7.5%), bronchitis (10.0%), pneumonia (7.5%), cytomegalovirus infection reactivation (5.0%), implant site infection (5.0%), and laryngitis (5.0%). A total of 10 patients (25.0%) experienced infections of Grade 3 or 4, and 10 patients (25.0%) experienced serious infections. At the time of analysis, using the March 16, 2022 data cut-off, proportions of patients with hypogammaglobinemia were not reported. A total of 4 patients (10%) experienced ICANS. All cases of ICANS were concurrent with CRS events, and no patients discontinued treatment due to ICANS. A total of 35 patients (87.5%) in Phase 2 Cohort C experienced at least 1 treatment-emergent cytopenic event, including neutropenia (67.5%), aneamia (50.0%), thrombocytopenia (45.0%), and lymphopenia (45.0%). Hemorrhagic events were reported for 5 patients (12.5%), 1 of which was of Grade 2.

Findings from the Phase 2 Cohort C of the MajesTEC-1 study were consistent with the results from the pivotal cohort (Phase 1 and Phase 2 Cohort A); however, only 40 patients were included, which limits interpretation of the cohort findings. Since the patients who took part in Phase 2 Cohort C were from the MajesTEC-1 study, it is reasonable to expect that the same limitations of the pivotal MajesTEC-1 study (Phase 1 and Phase 2 Cohort A) with respect to internal and external validity are relevant to Phase 2 Cohort C of MajesTEC-1.

Long-Term Extension Studies

No long-term extension studies were submitted by the sponsor.

Indirect Comparisons

The efficacy and safety of teclistamab among adult patients with RRMM who received at least 3 prior lines of therapy have been previously assessed in the MajesTEC-1 study. However, no head-to-head evidence of teclistamab compared against other treatments for RRMM was available for this review. Due to this gap in evidence, the sponsor submitted 6 indirect treatment comparisons (ITCs), of which 3 ITCs submitted by the sponsor were used to inform the pharmacoeconomic model, including 2 ITCs comparing the relative efficacy of teclistamab with real-world physician's choice (RWPC) therapy (from LocoMMotion and Daratumumab trials), and another ITC comparing the relative efficacy of teclistamab with ciltacabtagene autoleucel (from CARTITUDE-1). Of the 3 ITCs submitted by the sponsor, which were not included in the pharmacoeconomic model, 1 published ITC compared the relative efficacy of teclistamab with RWPC therapy (from Flatiron Health database), and 2 conference abstracts compared the relative efficacy of teclistamab with belantamab mafodotin (from DREAMM-2), and selinexor in combination with dexamethasone (from STORM Part 2). No systematic review was reported by the sponsor.

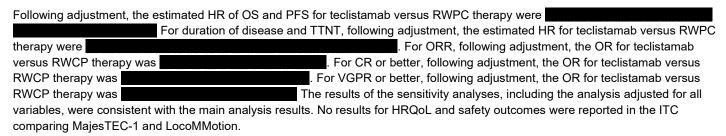## Sponsor-Submitted ITCs Used to Inform Pharmacoeconomic Model

Three ITCs that were used to inform the pharmacoeconomic model were selected because they met the selection criteria. The sponsor stated that they included the most relevant comparators for the submission, including treatments that are reimbursed in Canada or have received a recommendation for reimbursement from CADTH for the indication under review. Given the absence of a comparator group in the MajesTEC-1 study, an external control group was used to establish comparative efficacy of teclistamab versus treatments used in current clinical practice. To estimate the comparative efficacy, an inverse probability of treatment weighting (IPTW) estimator of the average treatment effect in the treated (ATT) was chosen for the main ITC analyses. This propensity score-based method allowed the RWPC cohorts from LocoMMotion, and Daratumumab trials cohort, as well as the population in CARTITUDE-1 to be reweighted to match the MajesTEC-1 population. There was sufficient overlap between patient characteristics between MajesTEC-1 and LocoMMotion, CARTITUDE-1, 4 Daratumumab trials (APOLLO, POLLUX, CASTOR, and EQUULEUS) to justify weighting techniques that do not depend on matching or excluding incompatible subpopulations. Propensity scores were estimated under an assumed logistic regression model using each cohort (MajesTEC-1, LocoMMotion, CARTITUDE-1, and Daratumumab trials cohort [APOLLO, POLLUX, CASTOR, and EQUULEUS]) as the dependent variable and selected baseline covariates as independent variables. The estimated propensity scores were then used to derive weights for each participant using the appropriate weighting formulas for the desired target population.

To ensure that the most important clinical factors were balanced between populations, an evidence-informed process (through a literature review of studies conducted to identify clinical outcomes in triple-class exposed patients with RRMM, and input from clinical experts) was used to select the prognostic factors for adjustment. In 2 ITCs comparing the relative efficacy of teclistamab with real-world patient's choice (RWPC) therapy from LocoMMotion and ciltacabtagene autoleucel from CARTITUDE-1, treatment weights were re-scaled to sum up to the original number of participants in the comparator studies. For the binary outcomes (e.g., ORR, CR response or better, VGPR response or better), a weighted logistic regression was used to derive an estimate of a conditional OR and the corresponding 95% CI, transformed to response-rate ratio (RR). For the time-to-event outcomes (e.g., PFS, duration of response, TTNT, and OS), a weighted Cox proportional hazards model was used to derive an estimate of the HR and the corresponding 95% CI. Appropriateness of the proportional hazards assumption used in the estimation of the HR of the survival outcomes was assessed based on visual inspection of the log-cumulative hazard plot, visual inspection of the Schoenfeld residuals plot, and performance of the Grambsch-Therneau test (with a P value less than 0.05 considered to indicate a violation of the assumption).

Teclistamab (MajesTEC-1) versus RWPC (LocoMMotion)

MajesTEC-1 (n = 165) is an ongoing, phase 1/2, multicenter, open-label, single-arm study. Eligible patients must have received a diagnosis of MM under IMWG diagnostic criteria, and have prior exposure to at least 1 PI, 1 IMiD, and 1 anti-CD38 monoclonal antibody. In terms of efficacy outcomes, the primary outcome in MajesTEC-1 was ORR, secondary outcomes included PR or better response, VGPR or better response, CR or better response, OS, PFS, MRD negative rate, duration of response, TTR, and the exploratory outcome was TTNT. LocoMMotion (n = 248) is a prospective, non-interventional study of real-life standard of care in patients with a documented diagnosis of MM according to IMWG diagnostic criteria who have received at least 3 prior lines of therapy including at least PIs, iMiDs, and anti-CD38 monoclonal antibodies. The primary outcome in LocoMMotion was ORR, secondary outcomes included VGPR rate, CR rate, stringent complete response sCR rate, MRD-negativity rate, clinical benefit rate, duration response, TTR, TTNT, PFS, and OS. Approximately 90 unique treatment regimens were used in the LocoMMotion study, including corticosteroids, PIs, iMiDs, alkylating agents, and anti-CD38 monoclonal antibodies, and various combinations, reflecting the existing variety of real-life antimyeloma treatments in this population. A total of 17 prognostic factors that were identified a priori as important for population alignment were available from both populations. Before weighting, moderate (standardized mean difference [SMD] greater than 0.1 and less than or equal to 0.2) to substantial (SMD greater than 0.2) differences were observed for many of the variables included in the main IPTW analysis. After reweighting, observable differences remained in the intention-to-treat (ITT) populations with regards to refractory status, and time to progression on last regimen. Cytogenetic risk was considered an important risk factor, however, was not included in the main analyses due to a high level of missingness in the LocoMMotion cohort (37.1%). As the LocoMMotion population only included a low number of non-white patients, adding the race variable to the adjustment led to high weights for these patients and decreased balance for all the other variables.

Following adjustment, the estimated HR of OS and PFS for teclistamab versus RWPC therapy were ▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮ For duration of disease and TTNT, following adjustment, the estimated HR for teclistamab versus RWPC therapy were ▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮. For ORR, following adjustment, the OR for teclistamab versus RWCP therapy was ▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮. For CR or better, following adjustment, the OR for teclistamab versus RWCP therapy was ▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮. For VGPR or better, following adjustment, the OR for teclistamab versus RWCP therapy was ▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮ The results of the sensitivity analyses, including the analysis adjusted for all variables, were consistent with the main analysis results. No results for HRQoL and safety outcomes were reported in the ITC comparing MajesTEC-1 and LocoMMotion.

Critical Appraisal

The sponsor-submitted ITC comparing the relative efficacy of teclistamab with real-world patient's choice (RWPC) therapy from LocoMMotion had a number of limitations that challenge the internal and external validity of the findings. No systematic search was conducted to identify relevant studies; therefore, there is a risk of selection bias. There was variation in the design of the MajesTEC-1 and LocoMMotion studies, as MajesTEC-1 was a Phase 1/2 trial, while LocoMMotion was an observational, non-interventional study. Both studies were open label, so there is a risk of bias in the measurement of subjective outcomes, particularly PFS, and clinical response outcomes. Objective outcomes including OS should be unaffected by the open-label designs. The definitions of end points were similar across the studies; however, the median duration of follow-up was 14.1 months in MajesTEC-1, and 16.1 months in the LocoMMotion study[29]. PFS and the clinical response outcomes were assessed based on IMWG criteria by an independent review committee (IRC) in the MajesTEC-1 study and by an independent Response Review Committee in the LocoMMotion study to reduce bias. In MajesTEC-1, there was a high degree of concordance between ORR assessments by the IRC and by the computerized algorithm utilized. The sensitivity analysis of ORR based upon investigator assessment was consistent with the primarily analysis using IRC assessment based on IMWG response criteria, and similar comparisons were done with PFS in MajesTEC-1. The LocoMMotion study used a total of 90 different treatment regimens and given that not all treatment regimens are relevant to Canadian clinical practice in forth-line and beyond settings (e.g., daratumumab, ixazomib, melphalan), the study results may not be generalizable to Canadian clinical practice. There was notable heterogeneity in the populations of the MajesTEC-1 and LocoMMotion studies. Of the 17 prognostic factors that were identified a priori, 15 variables were considered in the IPTW analyses for adjustment. Cytogenetic risk was considered an important risk factor by clinical experts; however, was not included in the main analyses due to a high level of missingness in the LocoMMotion cohort (37.1%). The clinical experts consulted by CADTH noted that cytogenetic risk is an important prognostic factor, and omitting this factor could result in potential bias. After reweighting, populations from MajesTEC-1 and LocoMMotion were more balanced, except for observed differences persisting in refractory status and time to progression on the

final regimen. While the weighted populations were balanced with respect to known, measured prognostic factors it remains unclear whether other unmeasured clinically relevant variables were unaccounted for. The variables not included in the planned adjustment set (unknown or unmeasured prognostic factors) can result in residual confounding and bias the estimates. Assessment of residual bias was not performed or reported. Therefore, results of the IPTW analysis may be considered to have a high risk of residual bias; however, the magnitude and direction of any bias is unknown. In addition, the interpretation of the outcomes is challenging due to systematic differences in study design. The sponsor stated that due to a small sample size in MajesTEC-1 and LocoMMotion, a scaled ATT weighting approach was used so that treatment weightings were scaled so that they were summed to the original number of participants in the comparator studies. No information was reported in this IPTW analysis regarding the distribution of weights generated by the weighting process and the number of patients with extremely high and extremely low weights (including patients assigned zero weight). Therefore, it remains unclear if patients with zero weights (when there is no overlap with the target study) were excluded from the adjusted sample of the LocoMMotion study in accordance with the National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) Technical Support Document, and what was the effective sample size in LocoMMotion after reweighting to estimate the number of non-weighted patients. Thus, due to the lack of clarity, the evidence obtained from this IPTW analysis remains uncertain, limiting the interpretation and generalizability of the results. Several sensitivity analyses were conducted, and results of sensitivity analyses were consistent with the main analyses. For OS, PFS, TTNT, and clinical response outcomes, the results of the adjusted treatment comparisons were consistent across end points, favouring teclistamab over RWCP therapy, and this is consistent with the opinion of the clinical experts consulted for this review; however, these findings must be interpreted in the context of the methodological limitations of these studies. Safety outcomes were not analyzed in the ITC report, and no justification was provided, which precludes a balanced judgment of comparative benefit relative to comparative harms. Outcomes that are important to patients, such as HRQoL, were also not analyzed in this ITC.

Teclistamab (MajesTEC-1) versus Ciltacabtagene Autoleucel (CARTITUDE-1)

MajesTEC-1 (n = 165) is an ongoing, phase 1/2, multicenter, open-label, single-arm study. Patients in MajesTEC-1 received teclistamab at a recommended dose of 1.5 mg/kg SC once a week, followed by step-up doses of 0.06 mg/kg and 0.3 mg/kg. The index date in MajesTEC-1 was defined as date of first dose for MajesTEC-1. CARTITUDE-1 (n = 113) is an open-label, single-arm, phase 1b/2 clinical trial evaluating the safety and efficacy of ciltacabtagene autoleucel in adult patients with RRMM. Eligible patients were diagnosed with MM according to IMWG diagnostic criteria and must have received at least 3 prior lines of therapy or must be double-refractory to an IMiD and a PI. In CARTITUDE-1, following apheresis and premedication, ciltacabtagene autoleucel was administered as a single infusion dose of 0.75×10^6 CAR-positive viable T cells/kg. The primary outcome in CARTITUDE-1 was ORR, secondary outcomes included VGPR rate, CR rate, stringent complete response sCR rate, MRD negative rate, clinical benefit rate, duration response, TTR, TTNT, PFS, and OS. The ITT population in CARTITUDE-1 included all patients who underwent apheresis with the index date defined as the date of apheresis.

Before weighting, moderate to substantial differences were observed for many of the main analysis variables. After weighting, populations in MajesTEC-1 and CARTITUDE-1 were more balanced. After adjustment, differences remained in the ITT populations with regards to refractory status, age, hemoglobin level, and creatinine clearance. Following adjustment, the estimated HR of OS and PFS for teclistamab versus ciltacabtagene autoleucel were ███. Following adjustment, the estimated HR of duration of response for teclistamab versus ciltacabtagene autoleucel was ███████████ ███ Following adjustment, the estimated HR of TTNT for teclistamab versus ciltacabtagene autoleucel was █████████████████ ███████████████ No sensitivity analysis was performed in this ITC. No results for clinical response outcomes, including ORR, CR or better, and VGPR or better, were included in the study comparing MajesTEC-1 and CARTITUDE-1. No results for HRQoL and safety outcomes were included in the ITC comparing MajesTEC-1 and CARTITUDE-1.
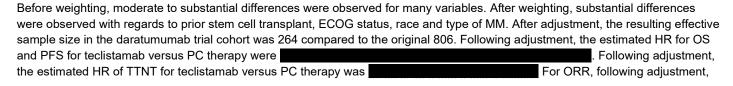
Critical Appraisal

No systematic search was conducted to relevant studies; therefore, there is a risk of selection bias. Both MajesTEC-1 and CARTITUDE-1 studies included in the ITC were presented with an unclear risk of bias for statistical analysis and a high risk for the measurement of subjective outcomes, such as PFS or clinical response outcomes, due to the open-label study design. Objective outcomes including OS should be unaffected by the open-label designs. The MajesTEC-1 cohort represented a broad population from Europe, Canada, and the US, whereas the results from CARTITUDE-1 are drawn from US patients only. Therefore, it is unclear whether differences in clinical practice or treatment availability exist across regions, and the direction and magnitude of potential

biases remain unclear. After weighting, populations in MajesTEC-1 and CARTITUDE-1 were more balanced, although observable differences remained between trials in refractory status, age, hemoglobin level, and creatinine clearance. While the weighted populations were balanced with respect to known, measured prognostic factors it remains unclear whether other unmeasured clinically relevant variables were unaccounted for. The variables not included in the planned adjustment set (unknown or unmeasured prognostic factors) can result in residual confounding and bias the estimates. Assessment of residual bias was not performed or reported. Therefore, results of the IPTW analysis may be considered to have a high risk of residual bias; however, the magnitude and direction of any bias is unknown. In addition, the interpretation of the outcomes is challenging due to systematic differences in study design and duration of follow-up. The sponsor stated that due to a small sample size in MajesTEC-1 and CARTITUDE-1, a scaled ATT weighting approach was used so that treatment weightings were scaled so that they were summed to the original number of participants in the comparator studies. No information was reported in this IPTW analysis regarding the distribution of weights generated by the weighting process and the number of patients with extremely high and extremely low weights (including patients assigned zero weight). Therefore, it remains unclear if patients with zero weights were excluded from the adjusted sample of the CARTITUDE-1 study in accordance with the NICE DSU Technical Support Document, and what was the effective sample size in CARTITUDE-1 after reweighting to estimate the number of non-weighted patients. Thus, due to the lack of clarity, the evidence obtained from this IPTW analysis remains uncertain, limiting the interpretation and generalizability of the results. No methods for handling missing data were performed or reported in the ITC comparing teclistamab this ITC. For OS, PFS, and TTNT, the results of the adjusted treatment comparisons were consistent across end points, favouring cltacabtagene autoleucel over teclistamab; however, these findings must be interpreted in the context of the methodological limitations of these studies. According to the clinical experts consulted by CADTH for this review, the population of CARTITUDE-1 was relatively healthy compared to the MajesTEC-1 population. Although all clinical response outcomes (ORR, CR or better, VGPR or better) were available in both studies, they were not assessed in this analysis. Safety outcomes were not analyzed in the ITC report, and no justification was provided, which precludes a balanced judgment of comparative benefit relative to comparative harms. Outcomes that are important to patients, such as HRQoL, were also not analyzed in this ITC.

Teclistamab (MajesTEC-1) versus Physician's Choice (PC) Therapy (APOLLO, POLLUX, CASTOR, and EQUULEUS)

MajesTEC-1 (n = 165) is an ongoing, phase 1/2, multicenter, open-label, single-arm study. Patients in the Daratumumab trials were triple-class exposed and were treated with physician's choice of therapy after discontinuing the trial treatments. The Daratumumab trials cohort was comprised of patients from the long-term follow-up data from POLLUX, CASTOR, EQUULEUS, and APOLLO. Because this ITC analysis retrospectively included patients participating in long-term follow-up clinical trials of daratumumab, it was possible to include patients in the earliest line of therapy initiated after all key selection criteria were met. However, this differed from the MajesTEC-1 study, in which patients may have received additional lines of therapy between the time at which they first met all eligibility criteria and the time at which they were enrolled into the clinical trial. To account for this difference, patients in the daratumumab trials became eligible for this analysis after having at least 3 prior lines of therapy, and patients who received multiple subsequent therapies after meeting eligibility criteria contributed multiple observations. Overall, 1,577 patients were initially included in the Daratumumab trials cohort, of which 642 patients were triple-class exposed and received at least 1 treatment regimen. Of the 642 patients, 427 patients with 806 eligible lines of therapy met MajesTEC-1 key inclusion criteria.[28] A total of 248 unique regimens were used in the RWCP from the Daratumumab trials cohort. The primary outcome in POLLUX was PFS, secondary outcomes included time to progression, VGPR response or better, MRD negative rate, ORR, OS, TTR, and duration of response. The primary outcome in CASTOR was PFS, secondary outcomes included time to progression, VGPR response or better, MRD negative rate, ORR, OS, and TTR. The primary outcome in EQUULEUS was proportion of adverse events and dose-limiting toxicities, secondary outcomes include ORR, OS, CR or better, and duration of response, exploratory outcomes included PFS, MRD negative rate, and pharmacokinetics. The primary outcome in APOLLO was PFS, secondary outcomes included VGPR or better, MRD negative rate, ORR, OS, duration of response, TTNT, and TTR. In the Daratumumab trials cohort, the index date was defined as the start of each eligible line of therapy.

Before weighting, moderate to substantial differences were observed for many variables. After weighting, substantial differences were observed with regards to prior stem cell transplant, ECOG status, race and type of MM. After adjustment, the resulting effective sample size in the daratumumab trial cohort was 264 compared to the original 806. Following adjustment, the estimated HR for OS and PFS for teclistamab versus PC therapy were ███████████████████████████████████████. Following adjustment, the estimated HR of TTNT for teclistamab versus PC therapy was ███████████████████████████ For ORR, following adjustment,

the OR for teclistamab versus PC therapy was ███████████ For CR or better, the OR for teclistamab versus PC therapy was ██ ███████████ For VGPR or better, following adjustment, the OR for teclistamab versus PC therapy was ███████████ Results from the fully adjusted scenario analysis were consistent with the main analysis results. No results for HRQoL and safety outcomes were included in the study comparing MajesTEC-1 and Daratumumab trial cohort.

Critical Appraisal

There was variation in the design of the MajesTEC-1 and 4 Daratumumab trials included in the IPTW analysis. MajesTEC-1 was a Phase 1/2 trial, while POLLUX, CASTOR, and APOLLO were open-label, phase III RCTs, and EQUULEUS was an open-label, non-randomized, phase 1b study. Both the MajesTEC-1 study and Daratumumab trials were open label, so there is a risk of bias in the measurement of subjective outcomes, particularly PFS, and clinical response outcomes. Objective outcomes including OS should be unaffected by the open-label designs. In addition, although 3 of the Daratumumab trials (POLLUX, CASTOR, and APOLLO) included in the ITC were randomized controlled trials (RCTs), and EQUULEUS was an open-label, non-randomized phase 1b study, patients selected from the Daratumumab trials cohort were included in the analysis retrospectively. A total of 248 unique treatment regimens were used in the Daratumumab trials cohort, of which, many were not relevant to Canadian clinical practice; thus, the study results may not be generalizable to the Canadian setting. There was notable heterogeneity in the populations of the MajesTEC-1 study and Daratumumab trials cohort. Nine of the 17 prognostic factors identified a priori were used for ATT weighting in the main analysis. After weighting, populations from the studies were balanced with respect to known, measured prognostic factors. While the weighted populations were balanced with respect to known, measured prognostic factors it remains unclear whether other unmeasured clinically relevant variables were unaccounted for. The variables not included in the planned adjustment set (unknown or unmeasured prognostic factors) can result in residual confounding and bias the estimates. Assessment of residual bias was not performed or reported. Therefore, results of the IPTW analysis may be considered to have a high risk of residual bias; however, the magnitude and direction of any bias is unknown. In addition, IPTW cannot adjust for differences related to other sources of heterogeneity, such as differences in study design, or median duration of follow-up. After adjustment, the effective sample size was reduced to approximately 32.8% (264/804) of the original sample size in the Daratumumab trials cohort. A small effective sample size implies that the estimates are being influenced by a subset of the patients from the Daratumumab trials and be caused by a violation of the transportability of the effects across cohorts. The proportional hazards assumption was tested for the time-to-event outcomes, and the Grambsch-Therneau test was significant for PFS and TTNT analyses, indicating potential violation of this assumption. The Cox proportional hazards model assumes that the HR across treatment groups does not change over time; therefore, violation of the proportional hazards assumption may lead to misleading and erroneous scientific conclusions. For OS, PFS, TTNT, and clinical response outcomes, the results of the adjusted treatment comparisons were consistent across end points, favouring teclistamab over PC therapy, and this is consistent with the opinion of the clinical experts consulted for this review; however, these findings must be interpreted in the context of the methodological limitations of these studies. Safety outcomes were not analyzed in the ITC report, and no justification was provided, which precludes a balanced judgment of comparative benefit relative to comparative harms. Outcomes that are important to patients, such as HRQoL, were also not analyzed in this ITC.

Other ITCs not Included in the Pharmacoeconomic Models

The ITCs submitted by the sponsor had a number of limitations that challenge the internal and external validity of the findings. No systematic search was conducted to identify the comparator studies included in the 3 ITCs that were not used to inform pharmacoeconomic models; therefore, there is a risk of selection bias. The selection criteria used to identify the comparator were consistent with the objective, and studies were included if they assessed treatment for RRMM, included patients with triple-class exposed RRMM who received at least 3 prior lines of therapy, and reported sufficient efficacy outcome data. However, no details were provided regarding the timing of the literature review, or the databases used. It is not possible to know whether the results may have differed if data from different RRMM studies or databases had been used. The list of excluded studies is not available, and the risk of bias of the included studies was not assessed. Given the absence of a comparator group in the MajesTEC-1 study, an external control group was used to establish relative efficacy of teclistamab versus treatments used in current clinical practice.

Teclistamab (MajesTEC-1) versus RWPC Therapy (Flatiron Health database)

An ITC using IPTW approach was conducted to assess the relative efficacy of teclistamab compared with RWPC therapy, using individual patient level data from the MajesTEC-1 trial (for teclistamab) and the nationwide de-identified electronic health record–derived Flatiron Health database (for the RWPC cohort). Key eligibility criteria of the MajesTEC-1 study were applied to the RWPC cohort, including a diagnosis of MM using IMWG criteria, prior exposure to 3 or more prior lines of therapy. Patients in the Flatiron cohort who received multiple subsequent therapies after meeting eligibility criteria contributed multiple observations to the ITC analysis. The MajesTEC-1 cohort included data from 165 patients, while the unadjusted population of the RWPC Flatiron Health cohort included 420 unique patients, corresponding to 766 eligible lines of therapy. The propensity score-based method of IPTW with an ATT weighting was used to reweight the RWPC Flatiron cohort to align with the MajesTEC-1 population and adjust for imbalances between patient populations. For the MajesTEC-1 trial, a clinical cut-off of March 16, 2022 was used, with the median duration of follow-up of 14.1 months. For the RWPC Flatiron cohort, patients who had 2 or more documented clinical visits on or after January 2011 were included, with the median duration of follow-up of 18.2 months. After weighting, the effective sample size of the RWPC Flatiron cohort reduced to 42.6% of the original population.

Following adjustment, the estimated HR of OS for teclistamab versus RWPC therapy from Flatiron cohort was 0.82 (95% CI, 0.59 to 1.14). For PFS, following adjustment, the estimated HR for teclistamab versus RWPC from Flatiron cohort was 0.43 (95% CI, 0.33 to 0.56). For TTNT, following adjustment, the estimated HR for teclistamab versus RWPC from Flatiron cohort was 0.36 (95% CI, 0.27 to 0.49). No results for safety and HRQoL were included in the ITC comparing MajesTEC-1 and Flatiron cohort.

As the Flatiron Health database was not selected using a systematic approach, there is a risk of selection bias. It is not possible to know whether the results may have differed if data from different RRMM studies or databases had been used. Numerous therapies were used in the RWCP groups from the Flatiron cohort, of which, many were not relevant to Canadian clinical practice; thus, may not be generalized to the Canadian setting. Additionally, patients included in the present analysis initiated eligible lines of therapy between 2016 and 2021; however, clinical practice has changed since the enrollment of patients from these sources and may not be reflective of current treatment standards in Canada. Patients selected from the Flatiron cohort were included in the analysis retrospectively. Data analyzed retrospectively from databases are prone to unique biases (e.g., selection bias, confounding) compared with those collected from prospective interventional studies, which cannot be controlled using IPTW methods. Outcomes in the MajesTEC-1 study were assessed by the IRC, while in the Flatiron cohort by the investigators; thus, the risk of bias in the outcome measurements is increased relative to the same outcomes as measured in the MajesTEC-1 study. The duration of follow-up in MajesTEC-1 was 14.1 months versus 18.2 months in the Flatiron cohort. There were important differences in the design of the studies including in this ITC, as the MajesTEC-1 study was phase 1/2 study, while the Flatiron cohort was a real-world cohort from electronic health records in the US, which limits the ability to draw strong conclusions about the efficacy of teclistamab relative to RWCP therapy due to differences in the clinician and patient behaviors, heterogeneity of treatments for intercurrent events and differences in data collection and intake. Such methodological differences could not be adjusted for in the IPTW analysis, and the magnitude and direction of any resulting bias is uncertain. There was evidence of heterogeneity between the population of the MajesTEC-1 and the Flatiron cohort. It remains unclear how balanced populations were for other variables that may be clinically relevant but could not be adjusted due to lack of data, or those variables that were not part of the planned adjustment (unknown or unmeasured prognostic factors), which leaves the potential for residual confounding. After weighting, the ESS of the Flatiron cohort was reduced by 57.4% from the included population. The reduction in the ESS reflects the heterogeneity between the trials among the variables including in the weighting process. Small effective sample size implies that the weighted estimates are being influenced by a subset of the patients from the Flatiron cohort that may not be representative of the entire study population, which may limit the generalizability of the results. For OS and PFS, the results of the adjusted treatment comparisons were consistent across end points, favouring teclistamab over RWPC therapy from the Flatiron cohort; however, these findings must be interpreted in the context of the methodological limitations of these studies.

Teclistamab (MajesTEC-1) versus Belantamab Mafodotin (DREAMM-2)

An unanchored MAIC was conducted to compare the efficacy of teclistamab with belantamab mafodotin using individual patient data from the MajesTEC-1 trial (n = 150) and summary-level data from the DREAMM-2 trial (n = 97). MajesTEC-1 was an open-label, single-arm, phase 1/2 study, while DREAMM-2 was an open-label, two-arm, phase 2 study. The DREAMM-2 eligibility criteria were applied to patients from the ITT population of MajesTEC-1. Compared to patients in the DREAMM-2 population, the MajesTEC-1

population had a higher proportion of patients who had ISS stage I disease. All patients had triple-class exposed RRMM who received at least 3 prior lines of therapy. Individual patient data from MajesTEC-1 were weighted to match the aggregated DREAMM-2 baseline patient characteristics. The following factors were used to adjust for imbalances between patient populations: refractory status, cytogenetic profile, ISS staging, presence of extramedullary disease, and number of prior lines of therapy. The effective sample size of MajesTEC-1 after propensity-score matching was 33 patients. Comparative efficacy of teclistamab relative to belantamab mafodotin was estimated for ORR, CR or better, OS, PFS, and duration of response. For binary outcomes, the relative effects were quantified using an OR and 95% CI derived from a weighted logistic regression analysis, while time-to-event outcomes were estimated using a weighted Cox proportional hazards model.

Following adjustment, the estimated HR for OS for teclistamab versus belantamab mafodotin was 0.95 (95% CI, 0.47 to 1.92). For PFS, following adjustment, the estimated HR for teclistamab versus belantamab mafodotin was 0.63 (95% CI, 0.34 to 1.15), and the estimated HR of duration of response was 0.19 (95% CI, 0.05 to 0.73). Following adjustment, the OR of ORR for teclistamab versus belantamab mafodotin was 2.05 (95% CI, 0.92 to 4.57), while the OR of CR or better was 2.13 (95% CI, 0.80 to 5.65). No results for safety and HRQoL were included in the ITC comparing the MajesTEC-1 and DREAMM-2 trials.

Critical appraisal

The open-label design of the studies can result in a risk of bias in the study conduct including the measurement of the outcomes, whether by unblinded assessor such as PFS and ORR, and the bias will likely favour the experimental intervention, although the extent of bias is uncertain. The effective sample size was reduced after adjustment in the MAIC analysis, and the effective sample size was reduced to approximately 22.0% (33/150) of the original population in the MajesTEC-1 study. The reduction in the ESS reflects the heterogeneity between the trials among the variables including in the weighting process. Small effective sample size implies that the weighted estimates are being influenced by a subset of the patients from the MajesTEC-1 study that may not be representative of the entire study population, which may limit the generalizability of the results. Populations from the studies were balanced with respect to known, measured prognostic factors. It remains unclear how balanced populations were for other variables that may be clinically relevant but could not be adjusted due to lack of data, or those variables that were not part of the planned adjustment (unknown or unmeasured prognostic factors), which leaves the potential for residual confounding. In the MAIC analysis, results in efficacy estimates were imprecise (i.e., wide confidence intervals) in the endpoints assessed (including HR = 1), and the upper and lower boundaries of the confidence intervals suggest the potential for different conclusions regarding the efficacy teclistamab relative to the comparator drugs. Therefore, no superiority conclusions could be drawn from the MAIC submitted by the sponsor due to methodological limitations and imprecision in the effect estimates.

Teclistamab (MajesTEC-1) versus Selinexor in Combination with Dexamethasone (STORM Part 2)

An unanchored matching-adjusted indirect treatment comparison (MAIC) was conducted to compare the efficacy of teclistamab with selinexor in combination with dexamethasone using individual patient data from the MajesTEC-1 trial (n = 150) and summary-level data from the STORM Part 2 trial (n = 122). The STORM Part 2 eligibility criteria were applied to patients from the ITT population of the MajesTEC-1 study. Compared to patients in the STORM Part 2 trial, the MajesTEC-1 population had a higher proportion of patients with R-ISS stage II. The 2 populations were similar in age, ECOG status, and cytogenetic status. All patients had triple-class exposed RRMM. After applying the STORM Part 2 eligibility criteria, individual patient data from patients in MajesTEC-1 were weighted to match the aggregated baseline patient characteristics from the STORM Part 2 trial. For binary outcomes, the relative effects were quantified using an OR and 95% CI derived from a weighted logistic regression analysis, while time-to-event outcomes were estimated using a weighted Cox proportional hazards model. The following factors were used to adjust for imbalances between patient populations: refractory status, cytogenetic profile, ISS staging, presence of extramedullary disease, and number of prior lines of therapy. The effective sample size of MajesTEC-1 after matching was 37 patients.

Following adjustment, the estimated HR of OS for teclistamab versus selinexor in combination with dexamethasone was 0.52 (95% CI, 0.28 to 0.95). Following adjustment, the estimated HR of PFS for teclistamab versus selinexor in combination with dexamethasone was 0.58 (95% CI, 0.30 to 1.11), and the estimated HR of duration of response was 0.04 (95% CI, 0.01 to 0.10). Following adjustment, the OR of ORR for teclistamab versus selinexor in combination with dexamethasone was 3.14 (95% CI, 1.48 to 6.69), while the OR of CR or better was 16.3 (95% CI, 3.5 to 77.1). No results for safety and HRQoL were included in the ITC comparing the MajesTEC-1 and STORM Part 2 trials.

Critical appraisal

The open-label design of the studies can result in a risk of bias in the study conduct including the measurement of the outcomes, whether by unblinded assessor such as PFS and ORR, and the bias will likely favour the experimental intervention, although the extent of bias is uncertain. The effective sample size was reduced after adjustment in the MAIC analysis, and the effective sample size was reduced to approximately 24.7% (37/150) of the original population in the MajesTEC-1 study. The reduction in the ESS reflects the heterogeneity between the trials among the variables including in the weighting process. Small effective sample size implies that the weighted estimates are being influenced by a subset of the patients from the MajesTEC-1 study that may not be representative of the entire study population, which may limit the generalizability of the results. It remains unclear how balanced populations were for other variables that may be clinically relevant but could not be adjusted due to lack of data, or those variables that were not part of the planned adjustment (unknown or unmeasured prognostic factors), which leaves the potential for residual confounding. In the MAIC analysis, results in efficacy estimates were imprecise (i.e., wide confidence intervals) in the end points assessed, and the upper and lower boundaries of the confidence intervals suggest the potential for different conclusions regarding the efficacy teclistamab relative to the comparator drugs. Therefore, no superiority conclusions could be drawn from the MAIC submitted by the sponsor due to methodological limitations and imprecision in the effect estimates.

Economic Evidence

Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned Survival Model (PSM)
Target population	Adult patients with relapsed/refractory multiple myeloma (RRMM), with greater than or equal to 3 prior lines of therapy including a proteasome inhibitor (PI), an immunomodulatory drug (IMiD), and an anti-CD38 monoclonal antibody (mAb), and who have demonstrated disease progression on the last therapy.
Treatment	Teclistamab
Dose regimen	The recommended starting dose is 0.06 mg/kg on day 1, followed by 0.3 mg/kg on day 3 and 1.5 mg/kg on day 5; 1.5 mg/kg is then given once weekly thereafter.
Submitted price	Teclistamab, 10 mg/mL (30 mg/3 mL) and 90 mg/mL (153 mg/1.7mL), solution for subcutaneous injection: $1,322 and $6,741 for 10 mg/mL and 90 mg/mL, respectively.
Submitted treatment cost	The first 28-day costs of teclistamab are $29,608. Every 28-days after this the costs are $26,964. This assumes a weight of 75kg.
Comparators	• Mix of currently reimbursed combination therapies (referred to as physician's choice): Kd (carfilzomib + dexamethasone) (33%); KCd (carfilzomib + cyclophosphamide + dexamethasone) (7%); Pd (pomalidomide + dexamethasone) (28%); PCd (pomalidomide + cyclophosphamide + dexamethasone) (32%). • Cilta-cel
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, life-years
Time horizon	Lifetime (30 years)
Key data sources	• Teclistamab: single-arm, phase I/II MajesTEC-1 trial (data cutoff: January 4, 2023). • Physician's choice: LocoMMotion prospective non-interventional study (data cut-off: October 2022). • Cilta-cel: single-arm, phase Ib/II CARTITUDE-1 trial (data cut-off: January 2022).
Submitted results	• ICER versus physician's choice = $454,345 per QALY gained (incremental costs = $468,254; incremental QALYs = 1.03). • ICER versus cilta-cel: teclistamab was less costly and less effective (incremental costs = -$84,129; incremental QALYs = -2.46).
Key limitations	• Based on clinical expert feedback, the overall survival associated with teclistamab is uncertain relative to physician's choice. This is due to the lack of randomized evidence, as well as the lack of robust long-term survival data beyond 2 years.

Component	Description
	• Based on clinical expert feedback, once weekly dosing of carfilzomib was more common in Canadian practice than the twice weekly dosing assumed by the sponsor. Since weekly dosing is associated with lower costs due to less frequent dosing, the cost of the Kd regimen was overestimated.
	• The cost used for a 4mg pomalidomide capsule was higher than the cost cited in most Canadian jurisdictions.
	• The generalizability of the modelled population to Canadian clinical practice is unclear. Relative to the MajesTEC-1 trial, patients with RRMM may be older, have poorer performance status, more advanced staging, and higher prevalence of comorbidities in clinical practice. It is uncertain how these and other confounders may influence the magnitude of benefit for teclistamab relative to physician's choice.
	• Based on clinical expert feedback, SVd is a relevant comparator for this indication. As this was not considered by the sponsor, the cost-effectiveness of teclistamab relative to SVd is unknown.
	• The sponsor assumed the longer a patient remains progression free, the greater the reduction in utility when progression occurs. This assumption was considered uncertain based on feedback from clinical experts.
CADTH reanalysis results	• For the CADTH base case, the cost of pomalidomide was updated and carfilzomib was assumed to be administered weekly rather than twice-weekly. Further uncertainties were explored in scenario analyses.
	• In the CADTH base case, teclistamab was more effective (incremental LYs: 1.37; incremental QALYs: 1.03) and associated with greater total costs (incremental costs: $522,024) than physician's choice. This resulted in an ICER of $506,518 per QALY gained. Relative to cilta cel, teclistamab was less costly and less effective (incremental costs = -$78,899; incremental QALYs = -2.46).
	• An 89% price reduction would be required for teclistamab to be considered cost-effective at a willingness-to-pay threshold of $50,000 per QALY gained relative to physician's choice.

Budget Impact

CADTH identified the following limitations in the sponsor's base case: the calculation of the budget impact analysis is uncertain; the proportion of patients with NDMM receiving therapy in fourth line is uncertain; the treatment schedule for carfilzomib + dexamethasone is not reflective of Canadian practice; the cost of pomalidomide is not reflective of most jurisdictions; the dosing schedule for teclistamab is uncertain; and the market share of teclistamab may be underestimated.

CADTH conducted reanalyses of the BIA by revising the calculation of the costs associated with teclistamab and physician's choice therapies; revising the eligible patient population; adopting a once weekly dosing schedule for carfilzomib + dexamethasone to once weekly; and adjusting the cost of pomalidomide. Based on the CADTH base case, the incremental expenditures associated with the reimbursement of teclistamab for the fourth-line treatment of adult patients with RRMM who have demonstrated disease progression on the last therapy, as per its reimbursement request, would be $30,276,140 in Year 1, $57,027,919 in Year 2, and $92,228,347 in Year 3, for a three-year cumulative total of $179,532,406. There is uncertainty in this estimate due to uncertain market uptake of teclistamab; the size of the RRMM population requiring a 4L therapy, and potential for dose switching.

pERC Information

Members of the Committee:

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Phillip 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: February 14, 2024

Regrets:

2 of expert committee members did not attend.

Conflicts of interest:

None