Canada's Drug Agency
L'Agence des médicaments du Canada

Reimbursement Review

CDA-AMC Reimbursement Recommendation

Draft

Daratumumab (Darzalex SC)

Indication: Daratumumab in combination with bortezomib, lenalidomide, and dexamethasone, followed by maintenance treatment in combination with lenalidomide, for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant.

Sponsor: Janssen Inc.

Recommendation: Reimburse with Conditions

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Single Technology

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Recommendation

The CDA-AMC pCODR Expert Review Committee (pERC) recommends that daratumumab in combination with bortezomib, lenalidomide, and dexamethasone (D-VRd), followed by maintenance treatment in combination with lenalidomide, be reimbursed for the treatment of adult patients with newly diagnosed multiple myeloma (NDMM) who are eligible for autologous stem cell transplant (ASCT) if conditions listed in **Error! Reference source not found.** are met.

Rationale for the Recommendation

Evidence from 1 phase III, open-label, active-controlled randomized controlled trial (PERSEUS, N = 709) demonstrated that treatment with D-VRd, followed by maintenance treatment with daratumumab plus lenalidomide, resulted in added clinical benefit in adult patients with NDMM who are eligible for ASCT, when compared to bortezomib-lenalidomide-dexamethasone (VRd) followed by maintenance treatment with lenalidomide. In the PERSEUS trial, treatment with D-VRd followed by maintenance treatment with daratumumab plus lenalidomide was associated with statistically significant and clinically meaningful improvements in progression-free survival (PFS) (hazard ratio [HR] = 0.42; 95% confidence interval [CI], 0.30 to 0.59), when compared to VRd followed by maintenance treatment with lenalidomide. Results for bone marrow minimal residual disease (MRD) negativity rate (75.2% for D-VRd versus 47.5% for VRd; odds ratio [OR] = 3.40; 95% CI, 2.47 to 4.69) and very good partial response (VGPR) or better rate (95.2% for D-VRd versus 89.3% for VRd; OR = 2.40; 95% CI, 1.33 to 4.35) were supportive of PFS findings.

Patients identified the need for effective, accessible treatment options with manageable side effects that can delay disease progression, prolong survival, deepen response, improve quality of life, and minimize psychological and financial burden for patients and caregivers. pERC noted that treatment with D-VRd met some of the patient needs, as it provides an additional treatment option with improved PFS, and likely results in improvement in treatment response. pERC agreed with the clinical experts that D-VRd has manageable toxicity profile with no significant detriment to health-related quality of life (HRQoL).

The cost-effectiveness of D-VRd varies depending on the availability of MRD testing in MM in Canada, which determines eligibility for discontinuation of maintenance therapy with daratumumab. Since MRD testing in MM is not currently part of the standard of care and is not uniformly available across jurisdictions, the incremental cost-effectiveness ratio (ICER) for D-VRd is $1,327,480 per quality-adjusted life-year (QALY) gained compared with VRd when patients are treated with maintenance therapy with daratumumab until progression. At this ICER, D-VRd is not cost-effective at a $50,000 per QALY gained willingness to pay (WTP) threshold for adult patients with NDMM who are transplant-eligible. A price reduction is required for the cost of daratumumab as part of the D-VRd regimen to be considered cost-effective at a $50,000 per QALY gained threshold. The cost-effectiveness of D-VRd would improve if MRD testing in MM became routine clinical practice in Canada. This is because MRD testing would allow for early treatment discontinuation in patients who no longer require maintenance therapy with daratumumab, reducing drug acquisition costs while preserving clinical benefit.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. D-VRd followed by maintenance treatment with daratumumab plus lenalidomide should be reimbursed in adult patients who meet all the following criteria: 1.1. eligible for ASCT 1.2. have received no prior systemic therapy for MM (other than corticosteroids) 1.3. have good performance status	In the PERSEUS trial, D-VRd demonstrated a clinical benefit in adult patients with NDMM for whom ASCT is part of the intended treatment plan. Patients in the PERSEUS trial had an ECOG performance status of 0 or 1.	pERC agreed with the clinical experts that patients with an ECOG performance status of more than 1 may be treated at the discretion of the treating physician.
2. Daratumumab should not be initiated in patients with clinical signs of meningeal involvement of MM	The CDA-AMC review did not include any evidence to demonstrate the benefit of induction, consolidation or maintenance therapy with daratumumab combination therapies in patients with NDMM exhibiting clinical signs of meningeal involvement as these patients were excluded from the PERSEUS trial.	—
Renewal		
3. Continued reimbursement of daratumumab should be based on the assessment of response to therapy according to: 3.1. clinical, laboratory and imaging assessments based on local standards for management of NDMM 3.2. presence of residual disease, as defined by detectable MRD, every 12 months during maintenance therapy	In the PERSEUS trial, evidence of response was assessed using clinical and laboratory assessment including bone marrow aspirate for evaluation of MRD status at 12, 18, 24, 30, and 36 months after the initiation of the trial treatment and yearly, thereafter.	pERC agreed with the clinical experts that there may be practical and patient preference-based limitations to frequent (i.e., more than 1 time per year) testing even though more frequent testing would provide a more precise real time assessment of the MRD status.
Discontinuation		
4. Treatment with daratumumab should be discontinued upon occurrence of any of the following: 4.1. disease progression 4.2. unacceptable toxicity attributed to daratumumab 4.3. achievement of CR or better and sustained MRD negativity for a minimum of 12 months after a minimum of 24 months of maintenance therapy with daratumumab plus lenalidomide	In the PERSEUS trial, the treatment phase consisted of 28-day cycles, including 4 cycles of induction, followed by ASCT, then 2 cycles of consolidation, followed by maintenance therapy until disease progression or unacceptable toxicity. After a minimum of 24 months of maintenance therapy, patients in the D-VRd group who had a response of CR or better discontinued therapy with daratumumab when sustained MRD negativity (at the threshold of 10^{-5}) was established for a minimum of 12 months.	pERC agreed with the clinical experts that MRD testing must be accessible in treatment centres to establish MRD negativity and assist in selecting the suitable patients for discontinuation of daratumumab. If the maintenance therapy with daratumumab is discontinued based on Condition 4.3, patients can continue lenalidomide maintenance therapy until disease progression or unacceptable toxicity.

Reimbursement condition	Reason	Implementation guidance
5. If one component of D-VRd and/or daratumumab plus lenalidomide is discontinued permanently because of tolerability concerns, the patient may continue to receive other components at the discretion of the treating physician, until the discontinuation criteria in Condition 4 are met	This condition reflects the treatment discontinuation criteria used in the PERSEUS trial.	—
Prescribing		
6. D-VRd followed by maintenance treatment with daratumumab and lenalidomide should be prescribed by clinicians with expertise in diagnosis and management of patient with MM	This is meant to ensure that D-VRd followed by maintenance treatment with daratumumab plus lenalidomide is prescribed for appropriate patients and that adverse effects are managed in an optimized and timely manner.	—
7. Daratumumab should be reimbursed when it is given in combination with VRd induction and consolidation treatment, and with lenalidomide during maintenance treatment	The PERSEUS trial demonstrated an added clinical benefit in adult patients with NDMM patients who received induction and consolidation treatment with D-VRd and maintenance treatment with daratumumab plus lenalidomide. pERC reviewed no evidence to support the efficacy and safety of monotherapy with Daratumumab, or its combination with other therapies.	—
Pricing		
8. A reduction in price	Since MRD testing in MM is not currently part of the standard of care and is not uniformly available across jurisdictions, the ICER for D-VRd is $1,327,480 per QALY gained compared with VRd. A price reduction of 84% would be required for the unit cost of daratumumab as part of the D-VRd regimen to achieve an ICER of $50,000 per QALY gained compared with VRd. If MRD testing were routinely conducted in MM in Canada, the ICER for D-VRd would be $460,578 per QALY gained when compared with VRd. A price reduction of 67% would be required for the unit cost of daratumumab as part of the D-VRd regimen to achieve an ICER of $50,000 per QALY gained compared with VRd. Notably, results from the analyses conducted by CDA-AMC may overestimate OS and PFS benefit, suggesting that even further price reductions beyond 84% may be required to ensure cost-effectiveness.	—

Reimbursement condition	Reason	Implementation guidance
Feasibility of adoption		
9. The economic feasibility of adoption of D-VRd must be addressed	At the submitted price, the incremental budget impact of D-VRd is expected to be greater than $40 million in years 1, 2, and 3.	—
10. The organizational feasibility of conducting MRD testing must be addressed.	MRD testing is required to determine eligibility for discontinuation of maintenance therapy with daratumumab. Since MRD testing for MM is currently not available in most of the clinical centres in Canada, use of MRD testing for discontinuation of maintenance therapy with daratumumab is anticipated to impact human and other health care resources. Nonetheless, it may also help reduce costs by avoiding unnecessary treatments, minimizing long term toxicities, and reducing the number of visits to cancer treatment centres to receive injections.	

ASCT = autologous stem cell transplant; CR = complete response; D-VRd = daratumumab-bortezomib-lenalidomide-dexamethasone; MRD = minimal residual disease; MM= multiple myeloma; NA = not applicable; NDMM = newly diagnosed multiple myeloma; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; VRd = bortezomib-lenalidomide-dexamethasone.

Discussion Points

- **Unmet needs:** pERC acknowledged the unmet need for more effective first-line treatments given that MM remains an incurable disease. It was noted that a substantial proportion of patients with MM do not respond to current first-line treatment options and will eventually relapse. pERC agreed with the patient group and clinicians that there is an unmet need for new effective therapies that are accessible and can result in deepened response, higher levels of MRD negativity, durable remission, prolonged survival, and improved HRQoL, while minimizing side effects. pERC additionally noted that patients with high-risk cytogenetics have lower response rates and shorter durations of response, and that these patients need more effective treatments.
- **Efficacy outcomes:** pERC noted that although 2 interim analyses and one final analysis were planned for PFS and overall survival (OS) in the PERSEUS, the analysis presented for this CDA-AMC review included data from August 1, 2023, data cut-off date for the first PFS interim analysis. The committee acknowledged that the median PFS and median OS were not reached for both D-VRd and VRd groups at the time of the interim analysis (after a median follow-up time of [redacted] months in the D-VRd group and [redacted] months in the VRd group). However, pERC noted that the evidence from the PERSEUS trial, which demonstrated with high and moderate certainty that D-VRd improves PFS, and MRD negativity and VGPR or better rates compared to VRd. pERC acknowledged the importance of clinical benefit in terms of OS to patients with MM and noted that OS benefit of adding daratumumab to VRd remains uncertain as the limited data from the PERSEUS trial showed that D-VRd likely may result in little to no difference in the probability of being alive at 48 months compared with VRd. pERC discussed that more patients in the VRd (control) group received subsequent anti-myeloma treatments compared to the D-VRd group, which might have led to the dilution of any OS benefit in the D-VRd group, despite a significant difference in PFS between the two groups.
- **Indirect evidence and studies addressing gaps in the systematic review:** No direct comparative evidence was submitted between D-VRd versus cyclophosphamide-bortezomib-dexamethasone (CyBorD), which is a relevant comparator according to the clinical experts consulted for this review. pERC discussed the results of 2 unanchored matching-adjusted indirect comparisons (MAICs) indirectly compared D-VRd against CyBorD. pERC noted that although indirect evidence showed that D-VRd, compared with CyBorD, was associated with improved PFS, the results were uncertain due to methodological limitations including differential duration of follow-up and the lack of adjustment for potential prognostic factors. The sponsor additionally provided results from a phase III, ongoing open-label RCT (AURIGA), to support the gap in comparative evidence of daratumumab-lenalidomide (daratumumab plus lenalidomide) versus lenalidomide alone as maintenance therapy after ASCT for NDMM, and 3 sponsor-conducted MAICs to address the aforementioned evidence gap. pERC noted the results from the AURIGA trial that suggested the addition to daratumumab to lenalidomide as maintenance therapy in patients who

had MRD positive disease at baseline resulted in benefits in the MRD conversion rate from baseline to 12 months, PFS, overall MRD (<1 x 10^5 negativity conversion rate from baseline, sustained MRD negativity rates at 6 and 12 months, and the overall CR or better response rate. However, the results were uncertain due to methodological limitations including open-label study design, imbalance in proportion of patients having high cytogenetic risk according to available local cytogenetic risk data at diagnosis, and handling of patients with missing or unevaluable data regarding MRD status in the primary end point analysis. pERC also noted that no definitive conclusions could be drawn from the submitted MAICs with respect to the relative effects of daratumumab plus lenalidomide versus lenalidomide due to important methodological limitations of the analyses.

- **MRD testing:** pERC agreed with the clinical groups and clinical experts consulted for this review that MRD testing is an emerging tool for response assessment in MM to enable treatment-related decisions based on sustained MRD negativity. In the PERSEUS trial, patients who achieved complete response or better and sustained a MRD negative status for a minimum of 12 months, after receiving a minimum of 24 months of maintenance therapy, could discontinue daratumumab maintenance while continuing treatment with lenalidomide. However, pERC noted that MRD testing for MM is currently not publicly funded and not part of standard of care in all jurisdictions in Canada. pERC acknowledged that testing capability is not available in most of the clinical centres in Canada, potentially presenting some barriers to implementing MRD-based treatment discontinuation criteria. Therefore, provision of MRD testing for daratumumab discontinuation in NDMM is anticipated to impact human and other health care resources. Nonetheless, pERC agreed with the clinicians that the use of MRD testing for discontinuation of maintenance therapy with daratumumab may also help minimize long term toxicities and reduce costs by avoiding unnecessary treatments and reducing the number of visits to cancer treatment centres (to receive injections and/or for the management of side effects). The committee agreed that upon implementation of the reimbursement recommendation for daratumumab for the indication under review, the jurisdictions would need to consider a common approach to ensure equitable patient access to MRD testing assays, with an acceptable level of sensitivity, to patients with NDMM who meet the eligibility criteria to receive D-VRd followed by maintenance therapy with daratumumab plus lenalidomide.
- **Economic considerations**: pERC identified substantial remaining uncertainty in the economic analysis, particularly due to immature trial data and assumptions related to MRD testing for MM in Canada. CDA-AMC explored alternative scenarios to assess the impact of treatment waning for PFS on the cost-effectiveness of D-VRd. pERC noted that if the effectiveness of D-VRd wanes earlier than the 20-year assumption underlying the base case, a larger price reduction would be necessary for the unit cost of daratumumab as part of the D-VRd regimen to be considered cost-effective at a $50,000 per QALY gained threshold. pERC also noted that the cost-effectiveness of D-VRd varies considerably based on the availability of MRD testing for MM in Canada. Since MRD testing is not currently part of the standard of care for MM and is inconsistently available across jurisdictions, the lifetime treatment costs for D-VRd increase by $624,724 per patient, resulting in an ICER exceeding $1.3 million per QALY gained compared with VRd. pERC acknowledged that the cost-effectiveness of D-VRd would improve substantially if MRD testing for MM became standard practice in Canada and emphasized the importance of securing dedicated funding to facilitate its implementation.

Background

Multiple myeloma (MM) is a hematological malignancy defined by plasma cell proliferation and excessive production of the abnormal immunoglobulin monoclonal protein (M-protein). Patients commonly experience fatigue and bone pain, as well as renal or nervous system problems, recurring infections, and fever. In Canada, an estimated 4,100 individuals had NDMM and approximately 1,750 deaths due to MM occurred in 2024 and it is estimated that there were 1,895 patients with transplant-eligible (TE) NDMM living in Canada as of 2024. Despite treatment advances in recent years, MM remains incurable, and patients face a poor prognosis with a five-year survival rate of approximately 50%. Moreover, most patients with MM relapse and many develop refractoriness to commonly used treatments. However, treatment with ASCT among patients with NDMM is associated with significantly improved clinical outcomes and considered the standard of care for TE NDMM. According to the clinical experts consulted for this review, for patients with TE NDMM, the current treatment consists of a multi-phase approach including induction therapy, ASCT (with high-dose chemotherapy) with or without consolidation therapy, followed by maintenance therapy. Because patients are not cured and will eventually relapse, there is a need for new treatments that will result in deepened response, higher levels of minimal residual disease (MRD) negativity, and longer remissions.

Daratumumab has been approved by Health Canada for use in combination with bortezomib, lenalidomide (R), and dexamethasone, followed by maintenance treatment in combination with lenalidomide, for the treatment of adult patients with NDMM who are eligible for ASCT. Daratumumab is a fully human immunoglobulin G1 monoclonal antibody. It is available as single-dose vial solution for subcutaneous injection and the dosage recommended in the product monograph is 1800 mg.

Sources of Information Used by the Committee

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

- a review of one phase III, open-label, active-controlled randomized controlled trial in patients with NDMM who were eligible for ASCT included in the Systematic Review section; five indirect treatment comparisons; and one one phase III, open-label, active-controlled randomized controlled trial included in the Studies Addressing Gaps in Systematic Review Evidence section.
- patients' perspectives gathered by one patient group, Myeloma Canada
- input from public drug plans that participate in the reimbursement review process
- two clinical specialists with expertise diagnosing and treating patients with MM
- input from two clinician group(s), the Canadian Myeloma Research Group (CMRG) and OH-CCO's Hematology Cancer Drug Advisory Committee (OH-CCO Drug Advisory Committees)
- a review of the pharmacoeconomic model and report submitted by the sponsor

Perspectives of Patients, Clinicians, and Drug Programs

Patient Group Input

This section was prepared by the review team based on the input provided by Myeloma Canada.

CDA-AMC received one patient group input from Myeloma Canada. Myeloma Canada conducted a patient and caregiver survey regarding D-VRd for the treatment of patients with NDMM receiving an ASCT in Canada. The survey was available from September 26 to October 10, 2024, and was shared via email and social media by Myeloma Canada and the Leukemia and Lymphoma Society of Canada. Survey eligibility was determined by self-report of patients and caregivers regarding their experience with MM, that they (or the person they care for) were eligible for ASCT at the time of diagnosis and received an ASCT or were waiting to receive one as part of their first line of therapy. Upon verifying their eligibility for, or experience with, D-VRd, respondents were divided into three subsets, and correspondingly posed different questions. These subsets were as follows: (1) patients who would be eligible for treatment with D-VRd and their caregivers (i.e., newly diagnosed and have not yet received treatment); (2) patients who received first-line treatment with ASCT and their caregivers; (3) patients who had experience with D-VRd and their caregivers. The survey received a total of 84 responses. Of these, 18 responses were incomplete (i.e., a respondent did not finish answering survey questions), and 27 ineligible responses were removed from the dataset, thus leaving 39 complete and eligible responses in the survey.

When asked to rate the importance of controlling various MM-related symptoms, respondents most frequently rated bone issues (i.e., fractures, breaks, bone pain) as 'extremely important to control', followed by kidney problems, mobility, pain and infections. Respondents also most frequently noted that MM-related symptoms had an extreme impact on their ability to work, ability to travel, and ability to conduct volunteer activities. Of the 34 patients with MM who responded to the survey, 17 required the support of a caregiver to help manage MM- and treatment-related symptoms. Of these 17 patients, three indicated that they were unable to access the support they needed.

The results of the survey highlighted several financial implications related to treatment for MM. Surveyed patients and caregivers most frequently noted the loss of income or pension funds due to absence from work, disability or early retirement as a significant financial implication related to MM treatment. Other common significant financial implications noted were parking costs, drug costs, and travel costs. The results of the survey also noted negative psychosocial impacts associated with treatment for MM. Of the various psychological and social difficulties related to MM, patients and caregivers most frequently rated the interruption of life goals and accomplishments (e.g., career, retirement, etc.) as having an extreme impact on their QoL. Other psychological and social difficulties related to MM that were frequently noted to have significant to extreme impacts on QoL were anxiety, difficulty sleeping, and loss of sexual desire.

Patients and caregivers completing the survey were asked to identify the factors that they consider to be the most important to MM treatment. The results of the survey found that the key factors were the effectiveness of treatment and achieving a long remission;

maintenance of QoL and mental health; management of side effects; portability of treatment to reduce the number of visits to treatment centres and mitigate impact on day-to-day activities; and the cost and accessibility of treatment.

Among the subset of respondents who received first-line treatment with ASCT combined with a drug regimen other than D-VRd (n = 11), drug regimens received included: cyclophosphamide-bortezomib-dexamethasone (CyBorD), VRd, ixazomib plus lenalidomide and dexamethasone, lenalidomide monotherapy, lenalidomide plus dexamethasone, and a sequence of CyBorD, VRd, and thalidomide. When asked questions regarding the safety profile of D-VRd, respondents in this subset most frequently noted that they felt that it was 'slightly worrisome' compared to the safety profiles of other treatment options available to them or the person that they cared for. When asked about their perceptions of the advantages and disadvantages of D-VRd compared to past treatment received, respondents noted that they believed that D-VRd would result in increased control of MM and its symptoms and improve QoL. However, they also noted that treatment would increase the frequency of trips to treatment centres. When asked similar questions about the safety profile of D-VRd, respondents who were deemed eligible for treatment with D-VRd (n = 6) most frequently noted that it was 'somewhat worrisome' compared to other available treatment options. Respondents also noted treatment side effects, frequency of trips to receive treatment, and tolerability of the mode of administration as factors that would impact QoL. Regarding the most common side effects for D-VRd, respondents from both subsets most frequently rated infections as 'not at all bearable' or 'slightly bearable', followed by nausea, fever, and diarrhea. Nonetheless, based on their knowledge at the time of the survey, respondents from both subsets most frequently indicated that they would have been interested in receiving D-VRd as first-line treatment for themselves or the person they care for.

Twenty-two respondents had prior treatment experience with D-VRd. When asked to indicate and rate their experienced side effects while receiving D-VRd, respondents most frequently rated diarrhea as 'not at all bearable' or 'slightly bearable', followed by infections and neuropathy. Of note, one patient reported stopping treatment with D-VRd due to rapid vision deterioration. Respondents also noted that supportive care received was effective to some degree in managing side effects related to D-VRd. Respondents who had prior treatment experience with D-VRd most frequently felt that treatment side effects had significantly impacted their quality of life, whereas the frequency of trips to receive treatment and tolerability of the mode of administration had somewhat impacted their quality of life. Nonetheless, most respondents indicated that treatment with D-VRd improved their overall QoL and side effects of D-VRd were mostly manageable. Most respondents also noted that treatment with D-VRd was effective in controlling MM and met their expectations in treating MM. Of note, respondents had access to D-VRd treatment through various avenues, which included compassionate access, clinical trials, insurance coverage (e.g., private or public provincial), access through a doctor, and self-funding. However, few respondents acknowledged that daratumumab was costly and emphasized the need for financial coverage to access treatment.

Myeloma Canada noted that the number of respondents to the survey who had experience with D-VRd was greater than previous surveys for other treatments, which suggests that D-VRd is already widely used in Canada. The results of the survey suggest that patients view D-VRd as an optimal treatment choice but also acknowledge that the regimen can be expensive due to the cost of daratumumab. Thus, patients who do not have access to private insurance or those who are unable to self-fund treatment may face barriers in accessing D-VRd. Myeloma Canada highlights the reimbursement of D-VRd as an equity issue and emphasizes its importance to ensure that patients in Canada have equal access to this treatment, regardless of socioeconomic status. Lastly, Myeloma Canada emphasized the importance of proactively informing patients about potential vision problems related to D-VRd, given that past surveys found that this side effect was of significant concern to patients. Proactively informing patients about potential vision problems and other side effects related to D-VRd would allow them to weigh their options and make an informed choice regarding treatment for MM.

Clinician Input

Input From Clinical Experts Consulted for This Review

All CDA-AMC review teams include at least 1 clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol, assisting in the critical appraisal of clinical evidence, interpreting the clinical relevance of the results, and providing guidance on the potential place in therapy). The following input was provided by 2 clinical specialists with expertise in the diagnosis and management of MM. *Unmet Needs*

The clinical experts consulted by CDA-AMC agreed that there is a substantial number of patients with MM who have suboptimal responses (incomplete or transient) to current first-line treatment options. Both experts agreed that there is a need for new treatments that will result in deepened response, higher levels of MRD negativity, and longer remissions among these patients. Of note, one expert cited concerns of eventual drug resistance and emergence of drug-resistant variants of disease related to continuous therapy. One expert also highlighted the need for patient education regarding incoming treatments for MM.

Place in Therapy

Daratumumab targets the underlying disease process for MM and according to the clinical experts consulted by CDA-AMC, daratumumab would be administered in combination with VRd as first-line therapy for MM and would be given wherever VRd is currently used for treating patients with NDMM. One expert noted that D-VRd would be given as an induction therapy prior to ASCT and as consolidation and maintenance therapy after ASCT. Of note, the experts did not recommend any alternative first-line regimens for patients with MM before initiating treatment with D-VRd.

Patient Population

According to the clinical experts consulted by CDA-AMC, D-VRd should be administered as a first-line therapy to patients with NDMM who are eligible for ASCT. One expert noted that age and health status were the most important factors in determining eligibility for ASCT and that less than 5% of patients who were 70 years of age or older would be eligible for transplant. It was also noted that eligibility for ASCT rarely changes after receipt of induction therapy. The clinical experts indicated that patients with MM would be identified by physicians with experience in treating MM. Of note, no issues related to the diagnosis or misdiagnosis of MM were identified. The clinical experts indicated that all eligible patients would benefit from treatment with D-VRd. They did not indicate a subgroup of patients that would receive more or less treatment benefit from D-VRd compared to other subgroups. The clinical experts also agreed that it was not possible to identify which patients would receive more or less treatment benefit from D-VRd.

The PERSEUS trial listed several exclusion criteria including (but not limited to) the presence of specified comorbidities (e.g., asthma, cardiac conditions, etc.), peripheral neuropathy, prior or concurrent non-MM related malignancy, meningeal involvement, and recent treatment with plasmapheresis or radiation therapy. It was agreed that the PERSEUS trial enrolled a more restrictive patient population compared to what is observed in clinical practice, given that patients would not be excluded from receiving treatment in clinical practice. However, one clinical expert indicated that patients excluded from the PERSEUS trial were overall less likely to be eligible for ASCT or receive treatment with D-VRd in clinical practice.

Assessing the Response to Treatment

The clinical experts indicated that the assessment of response to treatment for MM consists of regular monitoring of monoclonal protein via serum protein electrophoresis, serum FLC assays, and monitoring of standard disease parameters for MM. The experts agreed that assessment of response to treatment is performed monthly in clinical practice, although it was noted that it may be reduced to every 2 to 3 months for patients exhibiting stable disease response. They also agreed that bone marrow biopsy would be used to assess depth of response and would be performed at diagnosis, prior to ASCT and post-ASCT.

One clinical expert indicated that the definition of a clinically meaningful response to treatment depended on when it was assessed relative to the receipt of ASCT. For instance, a response of PR or greater achieved prior to ASCT was considered to be clinically meaningful but it would be expected that a patient would achieve a greater response than PR after receipt of ASCT. The other expert indicated that clinically meaningful responses to treatment also included reduction in MM-related symptoms (e.g., pain), improvements in key hematological outcomes (e.g., reduction or normalization of light chains and paraproteins, improvements in peripheral blood chemistry) and stabilization for improvement in bone imaging.

Discontinuing Treatment

The clinical experts consulted by CDA-AMC agreed that treatment with daratumumab would be discontinued in the event of disease progression or toxicity, although they noted that adverse events related to daratumumab were rare in clinical practice. These criteria were largely aligned with the discontinuation criteria for daratumumab in the PERSEUS trial. Of note, patients who achieved a CR or better response in the PERSEUS trial were only able to discontinue treatment with daratumumab if sustained MRD-negativity was established for a minimum of 12 months and after receipt of a minimum of 24 months of maintenance therapy. Although one clinical

expert suggested that sustained MRD negativity can be a potential criterion for discontinuation of daratumumab, they noted that this criterion is not formally used in clinical practice due to a lack of MRD testing across jurisdictions in Canada.

Prescribing Considerations

One clinical expert indicated that daratumumab can be prescribed and administered by any physician with experience treating MM in a variety of treatment settings, including rural and community settings. However, the other expert noted that subcutaneous daratumumab should be administered in established chemotherapy units by specialized hematologists or oncologists. They also noted that some infusion centers also have the expertise to administer this treatment. The expert also noted that chemotherapy units should be able to manage injection site reactions, although they were noted to be rare. Of note, one expert highlighted that access to qualifying specialists may vary across jurisdictions in Canada. Consequently, travel may be required of some patients, particularly those living in remote areas, in order to receive treatment.

Clinician Group Input

This section was prepared by the review team based on the input provided by clinician groups.

Clinician group input for this review was received from 2 clinician groups: the Canadian Myeloma Research Group (CMRG) and OH-CCO's Hematology Cancer Drug Advisory Committee (OH-CCO Drug Advisory Committees). A total of 33 clinicians (25 from CMRG and 7 from OH-CCO's Hematology Cancer Drug Advisory Committee) provided input for this submission.

Both the CMRG and OH-CCO Drug Advisory Committees agreed that goals for the treatment of MM include the achievement of anti-myeloma response, long-term control of MM-related disease and symptoms and prolonging of survival. The CMRG also highlighted the importance of minimizing treatment-related adverse effects and the improvement of QoL among patients with MM. Both clinician groups noted an unmet need related to current first-line treatment options for MM. Similar to the clinical experts consulted by CDA-AMC, the OH-CCO Drug Advisory Committees agreed that there exist patients with MM that do not respond adequately to first-line treatment. The CMRG highlighted the importance of first-line treatment, given that MM remains incurable. The CMRG also added that the majority of patients with MM experience their longest period of disease control during the first-line treatment, and that much of the improvements observed for long-term survival is dependent on maximizing disease control within this line.

The OH-CCO Drug Advisory Committees stated that D-VRd could become the new standard of care for TE NDMM. The CMRG noted that the addition of daratumumab to maintenance therapy may result in increased visits to cancer centres to receive injections. The CMRG also highlighted the importance of increasing the capacity of MRD testing in Canada to minimize long-term toxicity and financial and patient QoL burden related to daratumumab. They emphasized MRD testing as a valuable prognostic tool, as it can be used to identify patients who are expected to have very long-term disease control, which is expected to result in decreased MM-related morbidity and long-term healthcare utilization. The CMRG acknowledged that the implementation of widespread MRD testing would result in costs incurred to provincial jurisdictions. However, they noted that implementation will result in long-term cost savings for the health system, largely due to the de-escalation of daratumumab in eligible patients as confirmed by MRD testing.

Similar to the clinical experts consulted by CDA-AMC, both clinician groups agreed that patients with NDMM who are eligible for transplant would be best suited for treatment with D-VRd. The OH-CCO Drug Advisory Committees indicated that daratumumab can be delivered in any treatment setting with experience in administering the drug, which include community oncology clinics and medical facilities with expertise in administering cellular therapies for hematologic malignancies. The CMRG noted that daratumumab is appropriate for administration in outpatient settings, although consideration for funding the drug in inpatient settings may be required.

Both clinician groups agreed that standard myeloma and organ response criteria are used to assess response to treatment in clinical practice. The CMRG elaborated that the assessment of response is based on the tests for the monoclonal protein in the serum and urine, bone marrow biopsies, and imaging studies. In addition to these tests, MRD testing was noted as an emerging parameter of response assessment in MM. Similar to the clinical experts consulted by CDA-AMC, the CMRG indicated that clinically meaningful responses correlate with a PR or greater according to the IMWG Consensus Criteria, which would include improvement in MM-related symptoms and improvements in energy and ability to perform activities of daily living. The CMRG also indicated that response, in the context of MM, is assessed every 1-3 months depending on clinical stability and regimen used for treatment. Similar

to the clinical experts consulted by CDA-AMC, the OH-CCO Drug Advisory Committees and the CMRG agreed that treatment with daratumumab should be discontinued upon the occurrence of disease progression, unacceptable toxicity and/or intolerance.

Drug Program Input

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

Table 2: Responses to Questions from the Drug Programs

Implementation issues	Response
Relevant comparators	
The standard arm in the phase III PERSEUS trial used VRd induction (4 cycles) followed by ASCT and VRd consolidation (2 cycles), then lenalidomide maintenance therapy alone. In Canada, the standard of care is usually VRd or CyBorD induction (up to 4 cycles) followed by ASCT and one of either lenalidomide (more common) or bortezomib (less common) maintenance. VRd consolidation for 2 cycles after transplant is not commonly used. The choice of maintenance therapy is sometimes determined based on cytogenetics (e.g., some hematologists favor bortezomib maintenance in myeloma with del17p). Rarely, a second tandem transplant may be used as consolidation.	This is a comment from the drug programs to inform pERC deliberations.
Considerations for initiation of therapy	
Can daratumumab (or isatuximab) and/or lenalidomide be given to patients who relapse after maintenance therapy is discontinued? If so, what would be the appropriate progression-free interval for re-treatment? Should re-treatment with daratumumab (or use of isatuximab) be dependent on MRD status at time of discontinuation? Could daratumumab be re-started if the myeloma becomes MRD positive after previous MRD negativity, but no other signs of “classic” disease progression (see below for definitions)? Note: most jurisdictions follow clinical trial definitions for determining whether refractory to treatment for drug funding decisions – i.e., disease progression within 60 days of stopping treatment or progression on any dose, including progression while on maintenance therapy. These definitions include: Patients who experience an increase of 25% from lowest response value in one or more of the following are considered to have progressive disease: • serum M-component (the absolute increase must be 5 g/L)	The clinical experts consulted for this review stated that, depending on patient’s initial response to treatment, they would restart daratumumab (or isatuximab) for patients who stopped maintenance therapy due to reasons other than relapse (e.g., toxicity). pERC agreed with the clinical experts that patients who stop treatment because they are MRD negative would be eligible for retreatment with daratumumab if the treatment needs to be restarted after relapse. Patients who relapse on, or shortly (e.g. less than 3 months) after stopping, daratumumab would not be eligible for retreatment with daratumumab. pERC additionally agreed with the clinical experts that 90 days would be the appropriate progression-free interval for re-treatment of patients who stopped daratumumab for reasons other than disease progression. pERC agreed with the clinical experts that daratumumab can be re-started if the myeloma becomes MRD positive after previous MRD negativity, with no other signs of “classic” disease progression. One clinical expert commented that patients with very early MRD changes without signs of “classic” disease progression may be more responsive to retreatment. pERC further noted that no evidence regarding the efficacy and safety of treatment or re-treatment with isatuximab was included in the current review. The committee agreed that there may be a need for an updated provisional funding algorithm once

Implementation issues	Response
• urine M-component (the absolute increase must be 200 mg/24 h) • in patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved free light chain levels (the absolute increase must be >100 mg/L) • bone marrow plasma cell percentage (the absolute percentage must be >10%) • definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas • development of hypercalcemia (corrected serum calcium >2.65 mmol/L) that can be attributed solely to the plasma cell proliferative disorder	reimbursement recommendations are available for daratumumab and isatuximab.
Would patients with high risk cytogenetics (e.g., del17p, t(4;14), t(14;16) equally benefit?	pERC agreed with the clinical experts that patients with high risk cytogenetics (e.g., del17p, t(4;14), t(14;16) would equally benefit.
Should this regimen be available for patients with amyloidosis who would be considered eligible for ASCT?	The clinical experts consulted by the review team believed that this regimen should be available for patients with amyloidosis who would be considered eligible for ASCT. PERC discussed that patients with secondary amyloidosis with a myeloma diagnosis who are eligible for ASCT may be considered for treatment with D-VRd followed by daratumumab plus lenalidomide maintenance therapy. However, the committee was unable to comment on the efficacy of this treatment regimen for patients with primary light-chain amyloidosis, without evidence of concurrent multiple myeloma, as supporting evidence was not included in this review.
Considerations for discontinuation of therapy	
In the PERSEUS phase III trial, daratumumab maintenance was discontinued after a minimum of 24 months if MRD negative for at least 12 months. MRD testing in myeloma is not standard of care in Canada. Should the same discontinuation criteria apply in standard practice? What criteria should be used to assess response or to discontinue daratumumab if MRD testing is not available? If MRD testing is available and daratumumab is discontinued due to MRD negativity, can it be re-started if myeloma becomes MRD positive without other classical signs of disease progression (i.e., biochemical, clinical, radiological)? And if so, would daratumumab need to be re-loaded (weekly x 8 weeks, then bi-weekly x 4 months, then monthly, or would it be restarted at day 1 of an every 28 days cycle? This may have an impact on the BIA.	The clinical experts stressed that the availability of MRD testing is a key clinical consideration when deciding to discontinue maintenance treatment with daratumumab. However, it would be reasonable to apply the same daratumumab discontinuation criteria used in the PERSEUS trial to clinical practice only if centres have access to MRD testing that is as sensitive as the test used in the trial. Otherwise, therapeutic decisions for discontinuation of daratumumab after a minimum of 24 months may not be feasible. In the absence of an appropriate assay for MRD testing, the clinical expert anticipated that patients would stay on maintenance treatment with daratumumab plus lenalidomide until disease progression or unacceptable toxicity. pERC agreed with the clinical experts. pERC agreed with the clinical experts agreed that if MRD testing is available and daratumumab is discontinued due to MRD negativity, treatment can be re-started if patients' multiple myeloma becomes MRD positive without other classical signs of disease progression (i.e., biochemical, clinical, radiological).

Implementation issues	Response
	One clinical expert noted that retreatment with daratumumab would need to meet the therapeutic level in serum with weekly administrations before spacing out the treatments.
Note: lenalidomide was continued in the study until disease progression irrespective of MRD status. Should lenalidomide continue until disease progression in standard practice?	The clinical experts confirmed that lenalidomide should be continued until disease progression in standard practice. pERC agreed with the clinical experts.
Considerations for prescribing of therapy	
NA	
Generalizability	
Some patients with newly diagnosed plasma cell leukemia or amyloidosis are treated similarly to myeloma and receive an autologous stem cell transplant. Should this regimen be given to patients with newly diagnosed plasma cell leukemia or amyloidosis planned for autologous stem cell transplant?	The clinical experts agreed that patients with newly diagnosed plasma cell leukemia or amyloidosis planned for ASCT would be eligible for this regimen. However, they noted that the majority of patients with amyloidosis may not be transplant-eligible. PERC discussed that patients with amyloidosis who have a myeloma diagnosis may be considered for treatment with D-VRd followed by daratumumab plus lenalidomide maintenance therapy, if they are determined to receive ASCT. However, the committee was unable to comment on the efficacy of this treatment regimen for patients with primary light-chain amyloidosis without evidence of concurrent multiple myeloma, as supporting evidence was not included in this review.
Should daratumumab be added to induction or maintenance therapy for patients who are on alternate induction or maintenance regimens? If so, what is the timeframe to consider adding daratumumab to either induction or maintenance treatment?	pERC agreed with the clinical expert that, once approved, daratumumab could be added to the treatment regimen of patients who have started an alternative induction therapy . pERC agreed with clinical experts that there may be a time-limited need of adding daratumumab to the treatment for otherwise eligible patients who recently initiated treatment with VRd. However, pERC did not review any evidence to show the efficacy and safety of adding daratumumab to alternative regimens in patients NDMM who are ASCT-eligible. pERC also agreed with the clinical experts that daratumumab may be added to the treatment regimen for patients who have recently started maintenance therapy with lenalidomide (regardless of the type of induction and/or consolidation therapy regimen), at the discretion of the treating physician. The clinical experts' timeframe to consider adding daratumumab is rather arbitrary.
For patients who started VRd induction at time of implementation, would daratumumab be recommended to be added to induction, and if so, is there a maximum number of cycles in which one would consider before not adding daratumumab?	pERC agreed with the clinical experts that, at time of implementation of reimbursement recommendation, there may be a time-limited need for adding daratumumab to the treatment of patients who recently induction therapy with VRd. pERC agreed that the number of cycles would need to be individualised based on patients' response to treatment and timing of stem cell collection. pERC agreed with the clinical experts who suggested that it would be best for patients to receive at least 2 cycles of D-VRd pre-transplant even if that means adding cycles prior to stem cell collection or transplant.

Implementation issues	Response
Funding algorithm (oncology only)	
Request an initiation of a rapid provisional funding algorithm.	This is a comment from the drug programs to inform pERC deliberations.
Care provision issues	
MRD testing in multiple myeloma is not standard of care in Canada and is not available in all jurisdictions.	This is a comment from the drug programs to inform pERC deliberations.
Red blood cell genotyping is required for daratumumab and is available in jurisdictions.	This is a comment from the drug programs to inform pERC deliberations.
System and economic issues	
PAG is concerned about the potential large budget impact of daratumumab if recommended for newly diagnosed transplant-eligible myeloma.	This is a comment from the drug programs to inform pERC deliberations.
Confidential pCPA pricing exists for daratumumab for indications in the transplant-ineligible myeloma population. Generics are available for lenalidomide and bortezomib.	This is a comment from the drug programs to inform pERC deliberations.

ASCT = autologous stem cell transplant; CyBorD = cyclophosphamide-bortezomib-dexamethasone; CR = complete response; D-VRd = daratumumab-bortezomib-lenalidomide-dexamethasone; MRD = minimal residual disease; NA = not applicable; PAG = Provincial Advisory Group; pCPA = pan-Canadian Pharmaceutical Alliance; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; VRd = bortezomib-lenalidomide-dexamethasone.

Clinical Evidence

Systematic Review

Description of Studies

One phase III, open-label, active-controlled randomized controlled trial (RCT) (PERSEUS, N = 709) evaluated whether the addition of daratumumab to bortezomib-lenalidomide-dexamethasone (D-VRd) followed by maintenance therapy with daratumumab and lenalidomide prolong progression-free survival (PFS) compared to bortezomib-lenalidomide-dexamethasone (VRd) as induction and consolidation therapy followed by maintenance therapy with lenalidomide in patients with NDMM who are eligible for ASCT. The demographic characteristics were balanced between treatment groups. The median age of all patients was 60.0 years with a range of 31 to 70 years. Most patients were male (58.7%; female: 41.3%) and white (92.1%); 1.4% of patients were Asian, 1.3% of patients were Black, 0.6% of patients were Native Hawaiian or other Pacific Islander, and 0.4% of patients were American Indian or Alaska Native. At Baseline, most patients (63.6%) had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0. More than half (51.4%) of the patients had disease that was International Staging System (ISS) Stage I, and approximately one-fifth (21.7%) had high-risk cytogenetics such as del(17p), t(4;14), and t(14;16). The primary objective of the PERSEUS trial was to evaluate the efficacy of D-VRd compared to VRd in patients with TE NDMM in prolonging PFS. The secondary outcomes included CR or better rate (key secondary), MRD-negativity rate (key secondary), overall survival (OS) (key secondary),very good partial response (VGPR) or better rate, duration of response (DOR) (for CR or better response), and health-related quality of life (HRQoL) assessments. The study was funded by the European Myeloma Network in collaboration with Janssen Research and Development.

Efficacy Results

Only those efficacy outcomes identified as important for this review are reported. Efficacy and safety data were evaluated at a planned interim analysis with data cut-off date of August 1, 2023.

Progression-free Survival

At the time of the first interim analysis, the median duration of follow-up for PFS was [redacted] months (range [redacted] months to [redacted] months) in the D-VRd group, and [redacted] months in the VRd group (range [redacted] months to [redacted] months). Fifty patients (14.1%) in the D-VRd treatment group and 103 patients (29.1%) in the VRd group experienced a PFS event; among them, [redacted] had disease progression and [redacted] died in the D-VRd group, and [redacted] had disease progression and [redacted] died in the VRd group. The median PFS was not reached

(95% CI, not estimable) for both the D-VRd and VRd groups. The Kaplan-Meier (KM) estimate of PFS probability at 48 months was 84.3% (95% CI, 79.5% to 88.1%) for the D-VRd group, and 67.7% (95% CI, 62.2% to 72.6%) for the VRd group, the between-group difference was [redacted] (95% CI, [redacted] to [redacted]). The PFS results were consistent across all pre-specified and additional sensitivity analyses and subgroup results except for patients in the 65 years or older.

Very Good Partial Response or Better Rate

The VGPR or better rate was 95.2% (95% CI, 92.4% to 97.2%) in the D-VRd group and 89.3% (95% CI, 85.6% to 92.3%) the VRd group, the between-group difference was [redacted] (95% CI, [redacted] to [redacted]). The stratified Cochran Mantel-Haenszel estimate of odds ratio (OR) was 2.40 (95% CI, 1.33 to 4.35; nominal P = 0.0029).

Overall MRD Negativity Rate

The proportion of patients reported to have negative overall MRD in bone marrow by next-generation sequencing (threshold of 10^{-5}) and a CR or better response was 75.2% (95% CI, [redacted]) in the D-VRd group and 47.5% (95% CI, [redacted]) in the VRd group, the between-group difference was [redacted] (95% CI, [redacted] to [redacted]). The Mantel-Haenszel estimate of OR was 3.40 (95% CI, 2.47 to 4.69; P < 0.0001).

Overall Survival

The median duration of follow-up for OS was [redacted] months (range [redacted] months to [redacted] months) in the D-VRd group, and [redacted] months in the VRd group (range [redacted] months to [redacted] months). Thirty-four patients (9.6%) in the D-VRd treatment group and 44 patients (12.4%) in the VRd group had died. The median OS was not reached (95% CI, not estimable) for both the D-VRd and VRd groups. The KM estimate of OS probability at 48 months was 89.4% (95% CI, 85.4% to 92.4%) for the D-VRd group, and 87.5% (95% CI, 83.5% to 90.6%) for the VRd group, the between-group difference was [redacted] (95% CI, [redacted] to [redacted]).

Duration of Response (for complete response or better response)

The median DOR (for CR or better response) was not reached in both the D-VRd and VRd groups. Among patients who had a CR or better response (312 vs. 248 for D-VRd vs. VRd), [redacted] patients ([redacted]) in the D-VRd group and [redacted] patients ([redacted]) in the VRd group achieved CR or better but developed disease progression or died due to disease progression, [redacted] patients ([redacted]) in the D-VRd group and [redacted] patients ([redacted]) in the VRd group were censored. The KM estimate of event-free probability at 42 months was [redacted] (95% CI, [redacted] to [redacted]) in the D-VRd group and [redacted] (95% CI, [redacted] to [redacted]) in the VRd group, the between-group difference was [redacted] (95% CI, [redacted] to [redacted]).

Change from Baseline in EQ-5D-5L Utility Score

At baseline, the mean EQ-5D-5L utility score was [redacted] (SD = [redacted]) in the D-VRd group and [redacted] (SD = [redacted]) in the VRd group. At Maintenance Cycle 34 (approximately 40 months of treatment), patients in the D-VRd group reported a (LS) mean increase (increase reflects improvement) from baseline in the EQ-5D-5L utility score of [redacted] (SE = [redacted]) compared to [redacted](standard error [SE] = [redacted]) in patients in the VRd group, the between-group difference was [redacted] (95% CI, [redacted] to [redacted]; nominal P = [redacted]).

Harms Results

At the time of the first interim analysis (data cut-off: August 1, 2023), 349 of 351(99.4%) patients in the D-VRd group and 344 of 347 (99.1%) patients in the VRd group experienced at least one treatment-emergent adverse events (TATEs). The most common TEAEs were infections and infestations (86.9% vs. 76.7% for D-VRd vs. VRd), blood and lymphatic system disorders (83.2% vs. 73.2%), including neutropenia (69.2% vs. 58.8%), thrombocytopenia (48.4% vs. 34.3%), and anemia (22.2% vs. 20.7%), and gastrointestinal disorders (81.8% vs. 77.2%). Serious adverse events (SAEs) were reported among 57.0% of patients in the D-VRd group and 49.3% of patients in the VRd group with infections and infestations (35.0% vs. 27.4%) including pneumonia (11.4% vs. 6.1%) was the most reported SAE. Withdrawals due to TEAEs was reported among 116 patients (33.0%) in the D-VRd group and 104 patients (30.0%) in the VRd group. There were 34 (9.7%) patients in the D-VRd group and 43 (12.4%) patients in the VRd group died at the time of the first interim analysis. The most reported cause of death was disease progression (4.6% vs. 5.5%). The clinical experts identified notable harms including cytopenia, systemic administration-related reactions, and infections and infestations. Infections and infestations were observed in 305 (86.9%) patients in the D-VRd group and 266 (76.7%) patients in the VRd group. Cytopenia (comprising neutropenia, anemia, thrombocytopenia, and lymphopenia group terms) was reported in [redacted] ([redacted]) patients in the D-VRd

group and [redacted] ([redacted]) patients in the VRd group. Systemic administration-related reactions were defined as systemic reactions related to daratumumab subcutaneous administration., which reported in [redacted] ([redacted]) patients the D-VRd group, and the majority were Grade 1 or 2 events.

Critical Appraisal

The choice of VRd as the comparator in the PERSEUS trial was clinically relevant according to the clinical experts. The methods of randomization involved stratification using ISS at screening (I vs. II vs. III) and cytogenetics (standard risk vs. high risk) were considered appropriate. There was generally no notable imbalance in the baseline patient demographic and disease characteristics between treatment groups except for the involved FLC in serum, which was not a prognostic factor, according to the clinical experts consulted for this review, the impact of the imbalance in FLC levels would be minimal. As the PERSEUS trial is ongoing, results were only available from an interim analysis for this review. At the time of the interim analysis, the median PFS and median OS were not reached in both treatment groups. While there was an observed treatment benefit and trend towards an improved OS with D-VRd treatment, supported by improvements in MRD-negativity, the longer-term assessment of treatment effect in terms of both median survival time and hazard ratios is unknown. All patients in the D-VRd group received pre-administration medications (e.g., Antihistamines, corticosteroids, analgesics, and drugs for obstructive airway diseases) prior to receiving daratumumab to prevent infusion-related reactions whereas no patients in the VRd group received pre-injections. Although the clinical experts indicated that the use of pre-injections would not have an impact on the study results considering the adverse event prophylaxis effects of the pre-injected medications, the review team noted that the higher frequency of the use of pre-injections in the D-VRd group may bias the safety results in favour of D-VRd. Additionally, a higher proportion of patients in the D-VRd group used immune sera and immunoglobulins than the VRd group, this may bias the safety results in favour of the D-VRd group given immune sera and immunoglobulins could reduce the frequency of adverse events such as infections, as per feedback from the clinical experts. Fewer patients received subsequent treatment in the D-VRd group than the VRd group, this may be a potential source of bias for OS results against the D-VRd group. The benefit of D-VRd in terms of overall MRD negativity rate was likely over-estimated as a higher proportion of patients in the VRd group than the D-VRd discontinued treatment due to disease progression and patients who did not have the MRD negativity at a given time point were considered as MRD positive in the analysis. In the analysis of HRQoL measured using change from baseline in EQ-5D-5L utility score at Maintenance Cycle 34, a notably lower proportion of patients in the D-VRd group ([redacted]) than the VRd group ([redacted]) had lost to follow up at Maintenance Cycle 34 Day 1 (approximately 40 months of treatment), given adverse events and disease progression were the common reasons for treatment discontinuation, the disproportion of missing data between treatment groups would introduce bias in favour of the VRd group. Many of the outcomes used in the PERSEUS trial (PFS, MRD negativity rate, OS, VGPR or better rate, DOR, and HRQoL) were identified as clinically important by patients and/or clinicians, however, VGPR or better rate, DOR, and HRQoL were not part of the statistical testing strategy and thus were not adjusted for multiple testing, therefore, the ability to draw conclusions from these results may be limited.

The eligibility criteria of the PERSEUS trial were standard but more strict than clinical practice per feedback from the clinical experts. For example, patients aged 70 years or older were excluded; those patients could be candidates for D-VRd in clinical practice. The baseline characteristics of the PERSEUS trial may be indicative of the overrepresentation of patients who were White (92.1%) given the clinical experts indicated that there is a more diversified patients population including patients of other ethnic groups in their clinical practice. The proportion of patients who received consolidation therapy (75%) in the trial did not also seem to be reflective of clinical practice where, according to the clinical experts consulted for this review, less than half (50%) of patients would receive brief consolidation in clinical practice, given that consolidation therapy is not currently funded in all jurisdictions in Canada. These limitations may restrict the generalizability of the study results to clinical practice in Canada.

GRADE Summary of Findings and Certainty of the Evidence

For pivotal PERSEUS trial identified in the sponsor's systematic review, GRADE was used to assess the certainty of the evidence for outcomes considered most relevant to inform expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group. Following the GRADE approach, evidence from RCTs started as high-certainty evidence and could be rated down for concerns related to study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias.

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the

target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null.

The reference points for the certainty of evidence assessment for PFS, VRPR or better rate, overall MRD negative rate (at 10^{-5}), OS, DOR (defined as the duration of CR or better response), and harms were set according to the presence of an important effect based on thresholds agreed upon by clinical experts consulted by the review team for this review. For safety and HRQoL measured using EQ-5D-5L utility score, there is no established MID and the clinical experts could not provide a threshold of important difference so the target of the certainty of evidence assessment was the presence or absence of any (non-null) effect.

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members:

- Clinical outcomes (PFS, VGRP or better rate, overall MRD negativity rate, OS, and duration of CR or better)
- HRQoL
- Safety

Table 3: Summary of Findings for D-VRd Versus VRd for Patients With TE NDMM

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			VRd	D-VRd	Difference		
Progression-free survival							
Probability of being alive and progression-free at 48 months Follow-up (median): D-VRd: [redacted] months VRd: [redacted] months	709 (1 RCT)	HR = 0.42 (0.30 to 0.59)	677 per 1,000	843 per 1,000 (795 to 881 per 1,000)	[redacted] per 1,000 ([redacted] to [redacted] per 1,000)	High[a]	D-VRd results in a clinically important increase in the probability of patients being alive and progression-free at 48 months compared with VRd.
Very good partial response rate							
The proportion of patients who achieved a VGPR or better (CR, sCR, or VGPR) Follow-up (median): D-VRd: [redacted] months VRd: [redacted] months	709 (1 RCT)	OR = 2.40 (1.33 to 4.35)	893 per 1,000	952 per 1,000 (924 to 972 per 1,000)	[redacted] per 1,000 ([redacted] to [redacted] per 1,000)	Moderate[b,c]	D-VRd likely results in a clinically important increase in VGPR or better rate at 48 months compared with VRd.
Overall MRD negativity rate at 10^{-5} in bone marrow							
The proportion of patients who achieved overall MRD negative status (at 10^{-5})	709 (1 RCT)	OR = 3.40 (2.47 to 4.69)	475 per 1,000	752 per 1,000 ([redacted] to [redacted] per 1,000)	[redacted] per 1,000 ([redacted] to [redacted] per 1,000)	High[d]	D-VRd results in a clinically important increase in overall MRD negativity rate at 48 months compared with VRd.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			VRd	D-VRd	Difference		
Follow-up (median): D-VRd: [redacted] months VRd: [redacted] months							
Overall survival							
Probability of being alive at 48 months Follow-up (median): D-VRd: [redacted] months VRd: [redacted] months	709 (1 RCT)	HR = 0.73 (0.47 to 1.14)	875 per 1,000	894 per 1,000 (854 to 924 per 1,000)	[redacted] per 1,000 ([redacted] to [redacted] per 1,000)	Moderate[e]	D-VRd likely results in little to no difference in the probability of being alive at 48 months compared with VRd.
Duration of response (for CR or better reponse)							
Probability of remaining in response of CR or sCR at 42 months Follow-up (median): D-VRd: [redacted] months VRd: [redacted] months	675 (1 RCT)	HR = [redacted] ([redacted] to [redacted])	[redacted] per 1,000	[redacted] per 1,000 ([redacted] to [redacted] per 1,000)	[redacted] per 1,000 ([redacted] to [redacted] per 1,000)	Moderate[c,f]	D-VRd likely results in a clinically important increase in the probability of remaining in response of CR or sCR at 42 months compared with VRd.
Health-related quality of life							
LS mean change from baseline in EQ-5D-5L utility score at Maintenance Cycle 34 (approximately 40 months of treatment) Follow-up (median): D-VRd: [redacted] months VRd: [redacted] months	296 (1 RCT)	NR	[redacted] (NR)	[redacted] (NR)	[redacted] ([redacted] to [redacted])	High[c,g]	D-VRd results in little to no difference in the change from baseline in EQ-5D-5L utility score at Maintenance Cycle 34 (approximately 40 months of treatment) compared with VRd.
Harms							
Incidence infections and infestations at 48 months Follow-up (median): D-VRd: [redacted] months VRd: [redacted] months	698 (1 RCT)	NR	767 per 1,000	869 per 1,000 (NR)	102 per 1,000 ([redacted] to [redacted] per 1,000)	Moderate[c,h]	D-VRd likely results in a clinically important increase in the incidence infections and infestations at 48 months compared with VRd.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			VRd	D-VRd	Difference		
Incidence of cytopenia at 48 months Follow-up (median): D-VRd: [redacted] months VRd: [redacted] months	698 (1 RCT)	NR	[redacted] per 1,000	[redacted] per 1,000 (NR)	[redacted] per 1,000 ([redacted] to [redacted] per 1,000)	High[c,i]	D-VRd results in little to no difference in the incidence of cytopenia at 48 months compared with VRd.
Incidence of systemic administration-related reactions at 48 months Follow-up (median): D-VRd: [redacted] months VRd: [redacted] months	698 (1 RCT)	NR	NA	[redacted] per 1,000 (NR)	NA	NA	NA

CI = confidence interval; CR = complete response; EQ-5D-5L = EuroQol Group Five Dimensions Five Levels; NA = not applicable; MRD = minimal residual disease; NDMM = newly diagnosed multiple myeloma; NR = not reported; OR = odds ratio; PFS = progression-free survival; PR = partial response; RCT = randomized controlled trial; sCR = stringent complete response; SAE = serious adverse event; TN = transplant-eligible; VGPR = very good partial response.

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

[a] Imprecision was not rated down. There is no established between-group minimal important difference (MID) for PFS at 48 months, but the clinical experts considered that a 5% difference between groups in the probability of patients being alive and progression-free could be considered a threshold of clinical importance. The point estimate and the upper and lower bounds of the 95% CI for the between-group difference suggested a clinically important difference for D-VRd versus VRd based on a 5% threshold.

[b] Rated down 1 level for serious imprecision. There is no established between-group MID for VGPR or better rate at 48 months, but the clinical experts considered that a 10% difference between groups in the proportion of patients who achieved a VGPR or better (CR, sCR, or VGPR) could be considered a threshold of clinical importance. The point estimate and the lower bound of the 95% CI for the between-group difference suggested no clinically important difference between the two groups while the upper bound of the 95% CI suggested a clinically important difference for D-VRd versus VRd based on a 10% threshold. The statistical testing for VGPR or better rate was not adjusted for multiplicity in the PERSEUS trial and should be considered as supportive evidence.

[c] The statistical testing for this end point was not adjusted for multiplicity in analysis in the PERSEUS trial and should be considered as supportive evidence.

[d] Imprecision was not rated down. There is no established between-group MID for overall MRD negativity rate (at 10^{-5}) at 48 months, but the clinical experts considered that a 10% difference between groups in overall MRD negativity rate (at 10^{-5}) could be considered a threshold of clinical importance. The point estimate and the upper and lower bounds of the 95% CI for the between-group difference suggested a clinically important difference for D-VRd versus VRd based on a 10% threshold.

[e] Rated down 1 level for serious imprecision. There is no established between-group MID for OS at 48 months, but the clinical experts considered that a 5% difference between groups in the probability of patients being alive at 48 months, the point estimate and the lower bound of the 95% CI for the between-group difference suggested no clinical clinically important difference between the two groups while the upper bound of the 95% CI suggested a clinically important difference for D-VRd versus VRd based on a 5% threshold.

[f] Rated down 1 level for serious imprecision. There is no established between-group MID for duration of CR or better at 42 months, but the clinical experts considered that a 10% difference between groups in the probability of patients remaining in response (CR or sCR) at 42 months, the point estimate and the upper bound of the 95% CI for the between-group difference suggested a clinically important difference between the two groups while the lower bound of the 95% CI suggested no clinically important difference for D-VRd versus VRd based on a 10% threshold.

[g] Imprecision was not rated down. There is no established MID for change from baseline in EQ-5D-5L utility score and the clinical experts could not provide a threshold of important difference, so target of certainty appraisal was any effect for the change from baseline in EQ-5D-5L utility score at 48 months. The review team judged that the point estimate and 95% CI suggested no important difference between the two groups.

[h] Rated down 1 level for serious imprecision. There is no established between-group MID for the incidence of infections and infestations at 48 months, but the clinical experts considered that a 10% difference between groups in the incidence of infections and infestations at 48 months could be considered a threshold of clinical importance. The point estimate and the upper bound of the 95% CI for the between-group difference suggested a clinically important difference between the two groups while the lower bound of the 95% CI suggested no clinically important difference for D-VRd versus VRd based on a 10% threshold.

[i] Imprecision was not rated down. There is no established MID for the incidence of cytopenia at 48 months, but the clinical experts considered that a 20% difference between groups in the incidence of cytopenia at 48 months could be considered a threshold of clinical importance. The point estimate and the upper and lower bounds of the 95% CI for the between-group difference suggested no clinically important difference for D-VRd versus VRd based on a 20% threshold.

Source: Clinical Study Report for PERSEUS (2024) and sponsor provided additional information. Details included in the table are from the sponsor's Summary of Clinical Evidence.

Long-Term Extension Studies

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

Description of Studies

In the absence of head-to-head evidence to compare D-VRd with all relevant comparators, 5 sponsor-conducted indirect treatment comparisons (ITCs) in patients with TE NDMM were included in this review. Based on the results of a feasibility study, the sponsor noted that a lack of available studies with a common comparator to form a connected network made fitting a random-effect model, such as an network meta-analysis, infeasible. To compare D-VRd against CyBorD, the sponsor conducted 2 unanchored matching-adjusted indirect comparisons (MAICs), PERSEUS versus GMMG-MM5 and PERSEUS versus VCAT, to indirectly compare patient cohorts who received D-VRd with those who received CyBorD; the former study assessed patients who received the full treatment sequence (i.e., induction through maintenance treatments), while the latter study assessed patients who received induction through consolidation treatments. Three unanchored MAICs, PERSEUS versus Myeloma XI, PERSEUS versus IFM2005-02, and PERSEUS CALGB 100104, which indirectly compared daratumumab plus lenalidomide versus lenalidomide as maintenance treatments for patients with TE NDMM were also submitted. These 3 MAICs were conducted by the sponsor in an effort to assess the incremental benefit of adding daratumumab to the maintenance regimen consisting of lenalidomide alone given that in the PERSEUS trial, no re-randomization occurred upon initiation of maintenance treatment to minimize confounding. Of note, the maintenance studies included patients regardless of MRD response to induction through consolidation treatment. Individual patient data (IPD) from the D-VRd followed by daratumumab plus lenalidomide cohort of PERSEUS were matching-adjusted, based on relevant covariates identified in the literature or thorough expert opinion, to aggregate data from the comparator trials identified by a systematic literature review (SLR). OS and PFS were outcomes of interest. Balance between the populations in each comparison, after weighting, were assessed using the effective sample size (ESS) and the distribution of weights.

Efficacy Results

The effecitve sample size for the D-VRd group after match adjustment was [redacted] ([redacted] of the original sample size from PERSEUS) in the PERSEUS versus GMMG-MM5 study, and [redacted] ([redacted] of the original sample size from PERSEUS) in the PERSEUS versus VCAT study. The ESS for daratumumab plus lenalidomide group after match adjustment was [redacted] of the original sample size from PERSEUS, respectively) in the PERSEUS versus Myeloma XI, PERSEUS versus IFM2005-02, and PERSEUS versus CALGB 100104 studies, respectively.

D-VRd versus CyBord/VCd: Full Treatment Sequence

Following weighting, results of the PERSEUS versus GMMG-MM5 study were in favour of D-VRd compared with CyBord/VCd with respect to OS [redacted]) and PFS [redacted]).

D-VRd versus CyBord/VCd: Induction through Consolidation

Following weighting, PFS results of the PERSEUS versus VCAT study were in favour of D-VRd compared with CyBord/VCd ([redacted]. Results of the sensitivity analysis for PERSEUS versus VCAT were consistent with the base case. OS was not assessed in this ITC.

Daratumumab plus lenalidomide versus lenalidomide maintenance treatment

Following weighting, the difference in RMST between daratumumab plus lenalidomide and lenalidomide with respect to OS at 3 years of maintenance therapy was [redacted] in PERSEUS versus Myeloma XI, [redacted]) in PERSEUS versus IFM 2005-02, and [redacted]) in PERSEUS versus CALGB 100104. The difference in RMST between daratumumab plus lenalidomide and lenalidomide monotherapy with respect to PFS at 3 years of maintenance therapy was

[redacted]) in PERSEUS versus Myeloma XI[redacted]) in PERSEUS versus IFM2005-02, and [redacted]) in PERSEUS versus CALGB 100104.

Harms Results

Harms were not assessed in the ITCs.

Critical Appraisal

Studies included in the ITCs were identified by a sponsor-conducted SLR using appropriate methods. A feasibility assessment for a comprehensive ITC was subsequently conducted to inform study selection; however, reasons for study exclusion were not documented and as such, there is a potential risk of selection bias, although the extent of such bias is unclear. Other important limitations of the MAICs included inability to adjust for potential prognostic factors (e.g., ECOG performance status [not adjusted for in MAICs, except the PERSEUS versus VCAT study] and the presence of extramedullary plasmacytomas). As well, there were temporal discordance in study period between included studies, during which major changes in subsequent treatment pattern occurred and as a result, could be a potential source of bias for the OS results. The duration of follow-up differed between studies, which could potentially introduce bias in the comparisons of HR. Additional limitations of the 3 MAICs assessing maintenance treatments included heterogeneity in induction and consolidation regimens between studies and a lack of adjustment for MRD negativity rate at the baseline of maintenance therapy (not adjusted for in PERSEUS vs IFM 2005-02 and PERSEUS vs CALGB 100104), which was identified as an important prognostic factor for maintenance treatment. A sizable reduction in ESS ([redacted] of the PERSEUS cohort after the match-adjustment process was observed in the comparisons versus the VCAT, Myeloma XI, IFM2005-02, and CALGB 100104 studies, suggesting that there was a poor population overlap between studies and that the results may be heavily influenced by a subset of the sample in the PERSEUS trial who may not be representative of the full sample. MRD negativity rate, HRQoL, and harms outcomes, which are important to patients and clinicians, were not assessed in the analyses, representing a gap in evidence.

Studies Addressing Gaps in the Evidence From the Systematic Review

This section summarizes one RCT (AURIGA) that was submitted by the sponsor to address a gap in comparative evidence focusing on the use of daratumumab plus lenalidomide versus lenalidomide monotherapy, as maintenance therapy, for NDMM after ASCT.

Description of Studies

The AURIGA trial (NCT03901963) is a phase III open-label, active-controlled, multicenter RCT that evaluated the clinical benefit of adding daratumumab to maintenance treatment with lenalidomide among adult patients with TE NDMM who are MRD positive after induction therapy and ASCT. The AURIGA trial randomized 200 patients across 52 sites in the US and Canada to receive either daratumumab plus lenalidomide or lenalidomide as maintenance therapy for after induction and ASCT for TE NDMM. Eligible patients had NDMM, were treated with a minimum of 4 cycles of induction therapy and had received high dose therapy (HDT) and ASCT within 12 months of the start of induction therapy, with patients being within 6 months of ASCT on the date of randomization. Patients were also required to have a response of VGPR or better (assessed per IMWG 2016 criteria) at the time of randomization, residual disease as defined by detectable MRD, and an ECOG performance status score of 0,1, or 2.

Efficacy Results

Primary End Point

At the clinical cut-off date of April 4th, 2024, the MRD conversion rate from MRD positivity to MRD negativity (10^{-5}) from baseline to 12 months since the initiation of maintenance therapy was 50.5% in the daratumumab plus lenalidomide treatment group compared with 18.8% in the lenalidomide treatment group. The corresponding OR (daratumumab plus lenalidomide vs lenalidomide) was 4.51 (95% CI: 2.37 to 8.57), p-value <0.0001, which was statistically significant at the pre-specified 2-sided alpha level of 0.05.

Secondary End Points

At a median study follow-up time of 32.3 months, a total of 45 PFS events were observed. Of the 45 events observed, 19 were observed among the daratumumab plus lenalidomide treatment group and 26 were observed in the lenalidomide treatment group. The corresponding HR was 0.53 (95% CI: 0.29 to 0.97), demonstrating a 47% reduction in the risk of disease progression or death in

patients receiving daratumumab plus lenalidomide compared to those receiving R. The estimated 30-month PFS rates were 82.7% and 66.4% for the daratumumab plus lenalidomide and lenalidomide treatment groups, respectively. [22,23]

The overall MRD (10^{-5}) negativity conversion rate from baseline throughout the study treatment period was higher in the daratumumab plus lenalidomide treatment group compared to the lenalidomide treatment group (60.6% vs 27.7%), with a corresponding OR (daratumumab plus lenalidomide vs lenalidomide) of 4.12 (95% CI: 2.26 to 7.52) and p-value <0.0001.

The sustained MRD negativity rate at ≥6 months was higher in the daratumumab plus lenalidomide treatment group compared with lenalidomide treatment group (35.4% vs 13.9%), with a corresponding OR (daratumumab plus lenalidomide vs lenalidomide) of 3.40 (95% CI: 1.69 to 6.83) and a p-value of 0.0005. Similarly, the sustained MRD negativity rate at ≥12 months was higher in the daratumumab plus lenalidomide treatment group compared with lenalidomide treatment group (17.2% vs 5.0%), with a corresponding OR (daratumumab plus lenalidomide vs lenalidomide) of 4.08 (95% CI: 1.43 to 11.62) and a p-value of 0.0065.

At a median study follow-up time of 32.3 months, a total of 15 OS events were observed. Of the 15 events observed, 5 were observed in the daratumumab plus lenalidomide treatment group and 9 were observed in the lenalidomide treatment group. Median OS was not reached for either treatment group. The estimated 30-month OS rates were 94.6% and 91% for the daratumumab plus lenalidomide and lenalidomide treatment groups, respectively.

The overall CR or better response rate per IMWG criteria was higher in the daratumumab plus lenalidomide treatment group compared with the lenalidomide treatment group (75.8% [95% CI: 66.1% to 83.8%] vs 61.4% [95% CI: 51.2% to 70.9%]), with a corresponding OR (daratumumab plus lenalidomide vs lenalidomide) of 2.00 (95% CI: 1.08 to 3.69) and p-value of 0.0255.

Health-related quality of life, functioning, and symptoms were assessed using the EORTC-QLQ-C30, EORTC-QLQ-MY20, and the EQ-5D-5L questionnaires. Overall, there was no difference in HRQoL, symptoms, and functioning between the daratumumab plus lenalidomide and lenalidomide treatment groups and no detriment of HRQoL with the addition of daratumumab to maintenance therapy with lenalidomide.

Harms Results

The incidence of TEAEs in the AURIGA trial was 99% for both of the daratumumab plus lenalidomide and lenalidomide treatment groups. The most frequently reported TEAEs (incidence of 30% or higher in either arm) were neutropenia (daratumumab plus lenalidomide: 64.6%; R: 61.2%), diarrhea (daratumumab plus lenalidomide: 61.5%; R: 55.1%), and fatigue (daratumumab plus lenalidomide: 45.8%; R: 46.9%). Injection-related reactions were reported in 13.5% of patients in the daratumumab plus lenalidomide treatment group. Compared with the lenalidomide treatment group, patients in the daratumumab plus lenalidomide treatment group experienced higher incidences of grade 3/4 TEAEs (74.0% vs 67.3%) and serious TEAEs (30.2% vs 22.4%). Rates of discontinuation due to TEAEs were also higher in the daratumumab plus lenalidomide treatment group compared to the lenalidomide treatment group (12.5% vs 7.1%). Lastly, two deaths related to TEAEs occurred in the daratumumab plus lenalidomide treatment group and one TEAE-related death occurred in the lenalidomide treatment group.

Critical Appraisal

Strengths of the AURIGA trial included the stratification of patients by cytogenetic risk prior to randomization and the use of an ITT analysis to account for all randomized patients. A key limitation of the AURIGA trial was its open-label study design, which may have contributed to performance bias in results for patient-reported outcomes. Moreover, a larger proportion of patients in the daratumumab plus lenalidomide treatment group had high cytogenetic risk according to available local cytogenetic risk data at diagnosis (daratumumab plus lenalidomide: 23.9%; R: 16.9%). It was noted in the sponsor study report that any potential treatment effect due to this imbalance would have been in favor of the lenalidomide treatment group. Finally, subjects with missing or unevaluable MRD status were considered to have MRD positive status for the analysis of the primary end point. Given that a larger proportion of patients in the lenalidomide treatment group dropped out of the study, the imputation of all missing subjects as having MRD positive status would have likely biased results in favor of the daratumumab plus lenalidomide treatment group.

Although the AURIGA trial recruited patients living in the US and Canada, the trial results do not explicitly state the proportion of patients living in Canada nor provide a subgroup analysis of these patients. Although it may be argued that there are similarities between patients with MM living in Canada and those living in the US, it is unclear how representative the findings of the trial are to patients with MM living in Canada and being managed in clinical practice. Moreover, the trial only included patients who were MRD-

positive and who achieved a VGPR or better response after transplant. Clinical experts consulted by CDA-AMC indicated that patients who achieve a PR or better response are able to proceed with maintenance therapy as long as they do not show signs of progressive disease. Thus, the applicability of findings from the trial would be limited for this subset of patients. Lastly, the AURIGA trial also excluded patients who received daratumumab or other anti-CD38 therapies. Thus, the generalizability of the trial results may be limited for patients in the PERSEUS trial. This is important to note as the AURIGA trial was submitted to address the lack of evidence pertaining to efficacy of daratumumab plus lenalidomide as maintenance therapy from the PERSEUS trial. Of note, the results of the PERSEUS and AURIGA trials showed similar trends in terms of improvement in PFS, MRD negativity, and response associated with the addition of daratumumab to their respective regimens.

Testing Procedure Considerations

MRD status can be assessed using various methods, commonly next generation flow cytometry (NGF) and next generation sequencing (NGS). Both methods use a bone marrow aspiration sample. NGF-based MRD testing, developed by EuroFlow,[60] has been validated in real-world patients with MM as well as in clinical trials. NGS-based MRD testing (e.g., Adaptive clonoSEQ) is considered the gold standard and requires less sample than NGF does. NGS has high sensitivity that can be generalizable across institutions but requires a baseline sample for screening and identifying the predominant clonotype specific to each patient to monitor. NGF-based testing techniques can detect the presence of residual cancer cells with sensitivity thresholds up to 10^{-5} cells (i.e., 1 cancer cell among 100,000 bone marrow cells) and NGS-based testing techniques up to 10^{-6} cells (i.e., 1 cancer cell in 1 million bone marrow cells). Emerging technologies, such as mass spectrometry-based MRD testing using peripheral blood samples, are also being evaluated in Canada.

The CDA-AMC review team considered the potential impacts of MRD testing to ascertain eligibility for treatment discontinuation with daratumumab in adult patients with NDMM who are eligible for ASCT, upon the implementation of a reimbursement recommendation for daratumumab, including those on health systems, patients (and their families and caregivers), and costs. MRD testing in MM is currently not part of the standard of care, and NGF or NGS testing capability is not available in most of the clinical centres in Canada, potentially presenting some barriers if daratumumab becomes funded. Key considerations and relevant information available from materials submitted by the sponsor, input from the clinical experts consulted by the review team, and sources from the literature were validated by the CDA-AMC review team when possible and are summarized in Table 4.

Table 4: Considerations for MRD testing for establishing treatment discontinuation with daratumumab in newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant

Consideration	Criterion	Available Information
Health system-related	Number of individuals in Canada expected to require the test (e.g., per year)	The number of patients eligible for MRD testing would be the subset of incident NDMM patients who are transplant-eligible and would be eligible to receive daratumumab in the first line setting for induction, consolidation, and maintenance if daratumumab becomes funded. Assuming approximately 4,000 patients were diagnosed with MM in 2024, and about half of them were eligible for autologous stem cell transplant, the sponsor estimated that there would be [redacted] patients eligible to receive daratumumab in Canada per year. According to the clinical experts, this number might be an overestimate. Each patient would likely need to undergo MRD testing multiple times every year, adding to the total number of tests required. Thus, the total number of MRD tests expected to be conducted is dependent on the daratumumab uptake rate as well as the frequency and duration of testing.
	Availability and reimbursement status of the testing procedure in jurisdictions across Canada	NGS and NGF platforms and capabilities are available in some jurisdictions in Canada. However, MRD testing for MM is not publicly

Consideration	Criterion	Available Information
		funded, nor is MRD testing for MM routinely conducted in all jurisdictions in Canada. According to the sponsor, MRD testing for MM may be done at some sites on an as-needed basis. The sponsor estimated that there are 16 centres across the country (i.e., in British Columbia, Alberta, Saskatchewan, Ontario, Quebec, and Nova Scotia) that have capabilities to conduct MRD testing for MM. It is unclear whether NGS, NGF, or both technologies are available in these centres.
	Testing procedure as part of routine care	At the time of writing this report, MRD testing for MM is not routinely conducted in Canada.
	Repeat testing requirements	According to the clinical experts, MRD testing should ideally be initiated prior to treatment initiation with daratumumab and, once CR is achieved, repeated every 3 months during treatment with daratumumab. The experts noted the possibility of continued MRD testing even after daratumumab is discontinued, to detect relapse. 2025 guidance from a Canadian working group suggested MRD testing at 12 months post-therapy, but noted that the ideal time points for MRD testing in patients with MM who are transplant eligible were still being refined. Thus, the overall time for and frequency at which a patient needs to be monitored remains uncertain. The experts also highlighted the practical and patient preference-based limitations to frequent (i.e., more than 1 to 2 times per year) testing even though more frequent testing would provide a more precise real time assessment of the MRD status.
	Impacts on human and other health care resources by provision of the testing procedure	Based on the input from the clinical experts, provision of MRD testing for daratumumab discontinuation in NDMM if daratumumab becomes funded is anticipated to impact human and other health care resources. Since the testing is not routinely conducted currently and is only offered at a limited number of institutions on an ad-hoc basis, initial resources may be required for most institutions to establish testing (e.g., infrastructure, equipment) or to establish protocol or procedures for out-of-jurisdiction testing. There could be also impacts on human health care resources such as staffing needs and training of pathologists and other staff. Cancer Care Ontario/Ontario Health has identified several barriers in implementing MRD testing in other hematological cancers. These include financial impact, staffing, access to validated testing, and awareness in the community. These might be applicable to MRD testing in NDMM as well. Cancer Care Ontario/Ontario Health has also identified development of a structured reporting format and continued clinical evaluation for addressing some of the health care and patient-oriented considerations.
Patient-related	Accessibility of the testing procedure in jurisdictions across Canada	Currently, MRD testing is not publicly funded in Canada for MM. According to the sponsor, some institutions may offer and fund ad-hoc MRD testing. Even so, the clinical experts mentioned that the testing is not accessible to a large number of patients across the country. If daratumumab becomes funded, patients are likely to face barriers related to access to testing.
	Expected turnaround times for the testing procedure	According to the sponsor, for NGS-based MRD testing using Adaptive clonoSEQ offered by commercial laboratories outside of Canada, the

Consideration	Criterion	Available Information
		reported US laboratory standard of the turnaround time from sample receipt and reconciliation to result delivery is 7 days for fresh specimens and 14 days for stored specimens. NGF-based MRD testing has a shorter turnaround time, with results made available in a “few days”. It is uncertain if these turnaround times would apply to Canadian clinical settings. The clinical experts noted that a 2–4-week turnaround time would be acceptable for clinical decision making.
	Burden associated with the testing procedure for patients, families, and/or caregivers	NGS- and NGF-based MRD testing methods both require bone-marrow samples, which are collected using bone marrow aspiration, a relatively invasive and time-consuming procedure. Since multiple tests over and after the duration of treatment with daratumumab would be required, with new samples required at each time, patients would be required to visit the testing centre multiple times a year for sample collection. Patients may experience a psychological burden as they await their MRD testing results. In a small prospective patient survey, those with a MRD positive result felt disappointed and concerned about their prognosis, while those that were MRD negative felt more confident and optimistic. If daratumumab becomes funded, but MRD testing is not publicly funded or accessible, patients may experience a financial burden if the institution requires patients to pay out-of-pocket.
Clinical	Clinical utility and validity of the testing procedure	There is evidence to demonstrate the diagnostic accuracy and clinical utility of NGS- and NGF-based MRD testing methods in MM.[a] Furthermore, there is evidence to suggest the utility of MRD negativity, determined by these testing methods, as a tool to guide discontinuation of maintenance therapy in patients with MM.[a] Multiple studies have shown improved outcomes in patients who have achieved MRD negativity as assessed by one of these methods. In a large systematic review and meta-analysis encompassing 29 studies that assessed the MRD status by NGF and 9 studies by NGS, patients who tested MRD negative had significantly improved PFS and OS, compared with those who were MRD positive. These results were independent from the method of MRD evaluation.
	Risks of harm associated with the testing procedure	To test for the MRD status using NGS or NGF, samples are collected each time through bone marrow aspiration. Based on how often MRD testing is required to determine the potential for treatment discontinuation, patients might need to undergo bone marrow aspiration multiple times during and after treatment with daratumumab. While rare, patients may experience procedure-related adverse effects such as pain, excessive bleeding, infections, or rarely neurological damage due to nerve injury.
Cost	Projected cost of the testing procedure	Based on publicly available information, the cost of NGS using Adaptive clonoSEQ is approximately CA$2,500. The cost of NGF ranges from US$300-400. The clinical experts identified the cost of the tests as one of the main barriers to implementation.

ALL = acute lymphoblastic leukemia; MM = multiple myeloma; MRD = minimal residual disease; NDMM = newly diagnosed multiple myeloma; NGF = next generation flow cytometry; NGS = next generation sequencing; OS = overall survival; PFS = progression free survival.

[a] CDA-AMC have not evaluated or critically appraised this evidence to determine its validity or reliability.

Economic Evidence

Table 5: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis PSM
Target population	Adult patients with newly diagnosed MM who are transplant-eligible
Treatment	Daratumumab in combination with bortezomib, lenalidomide, and dexamethasone (referred to as D-VRd), followed by daratumumab plus lenalidomide in maintenance
Dose regimen	For each 28-day cycle: Cycle 1 and 2: 1,800 mg on days 1, 8, 15, and 22 Cycle 3 to 6: 1,800 mg on days 1 and 15 Cycles 7+: 1,800 mg on day 1
Submitted price	Daratumumab: $8,028 per single-dose vial
Submitted treatment cost	$37,005 per cycle 1 and 2; $20,949 per cycle 3 to 6; $9,215 per cycle 7+
Comparators	• Bortezomib + lenalidomide + dexamethasone (referred to as VRd) followed by lenalidomide maintenance • Cyclophosphamide + bortezomib + dexamethasone (referred to as CyBord) followed by lenalidomide maintenance
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (40 years)
Key data sources	• PERSEUS to inform comparative efficacy for D-VRd vs. VRd • Sponsor-conducted ITC to inform comparative efficacy for D-VRd vs. CyBord
Key limitations	• The sponsor's base case relied on a PSM structure which used immature OS data from the PERSEUS trial to extrapolate over a 40-year time horizon. In the absence of robust long-term data, PFS and OS beyond the trial data for D-VRd is uncertain. The sponsor's extrapolation of OS suggested over 50% of patients would have a mortality risk that matched the general population, which would only be plausible if MM was cured in the majority of patients. This was considered highly unlikely by clinical expert feedback received for this review. The analysis therefore overestimates long term survival. An alternative Markov model also submitted by the sponsor was considered more suitable as it produced more plausible estimates of long-term survival. • The sponsor assumed D-VRd treatment efficacy, expressed as a HR, would remain constant over time, meaning that treatment with D-VRd would permanently reduce the risk of progression and death for the remainder of the patient's life. Given that median PFS and OS were not achieved in the first interim analysis of the PERSEUS trial, there is uncertainty regarding the long-term treatment effect of D-VRd for patients with newly diagnosed MM who are transplant eligible. Clinical expert feedback received by CADTH noted that over time the cohort of progression free patients would become more homogenous between treatment arms and therefore the HR may trend to one over time. The sponsor's base case therefore likely overestimates the long-term benefit of D-VRd relative to VRd. • As per the PERSEUS trial, patients who achieved complete response or better and sustained MRD negative status at and beyond 24 months after starting maintenance therapy could discontinue daratumumab maintenance (but would remain on lenalidomide). Clinical expert feedback received by CADTH noted that based on current clinical practice across Canada, MRD testing is not routinely conducted. Therefore, using MRD status to inform treatment

Component	Description
	discontinuation may not be reflective of clinical practice in Canada and patients would remain on daratumumab. • The sponsor assumed no retreatment with an anti-CD38 for those who received DVRd in the first line and likewise 100% of patients who received VRd in the first line would receive an anti-CD38 as second line treatment. This assumption does not align with subsequent therapy usage in the trial or expectations from clinical experts consulted for this review. • In the absence of direct head-to-head evidence and limitations with the sponsor conducted ITC, the comparative clinical evidence of D-VRd versus CyBord is highly uncertain.
CADTH reanalysis results	• CADTH addressed key limitations with respect to model structure, extrapolation of OS, treatment waning, and subsequent therapy costs. Given the absence of long-term data, scenario analyses were conducted to explore uncertainties in these limitations. • In the CADTH reanalysis, based on the deterministic results, D-VRd was associated with an ICER of $460,578 per QALY gained compared to VRd (incremental cost: $315,884; incremental QALYs: 0.69). • Results from scenario analyses that explored alternative assumptions with treatment waning, subsequent therapies, and treatment of daratumumab until progression lead to a range of ICERs from $397,066 to $1,327,480 per QALY gained compared to VRd.

CyBord = cyclophosphamide + bortezomib + dexamethasone; D-VRd = daratumumab + bortezomib + lenalidomide + dexamethasone; ICER = incremental cost-effectiveness ratio; incr. = incremental; HR = hazard ratio; ITC = indirect treatment comparison; LY = life-year; MM = multiple myeloma; PSM = partitioned survival model; QALY= quality-adjusted life-year; VRd = bortezomib + lenalidomide + dexamethasone; vs. = versus.

Budget Impact

CADTH identified the following limitations in the sponsor's base case: market uptake of daratumumab is uncertain, treatment duration used to inform drug costs is uncertain, and the impact of D-VRd on subsequent therapy costs is uncertain. Based on the CADTH base case, the incremental budget impact of funding daratumumab SC for the treatment of adult patients with NDMM who are transplant eligible was $114,823,568 in Year 1, $274,958,778 in Year 2, and $436,019,907 in Year 3. Therefore, the 3-year incremental budget impact was $825,802,253. The short-term 3-year budget impact of treating until progression, versus discontinuing based on MRD negativity is similar. With treatment until progression, the 3-year BIA is $958,424,647, whereas early discontinuation of daratumumab based on MRD-based stopping rules reduces it to $933,470,968. This is because discontinuation rules take effect after 24 months, and most patients who discontinue daratumumab based on MRD negativity will do so around the 3-year mark. Beyond the 3-year time horizon, the budget impact difference will become substantially larger.

pERC Information

Members of the Committee:

This is a list that reflects the members of the committee at the most recent meeting, whether they actually attended or not.

Dr. Catherine Moltzan (Chair), Dr. Phillip Blanchette, Dr. Kelvin Chan, Dr. Matthew Cheung, Dr. Michael Crump, Annette Cyr, Dr. Jennifer Fishman, Dr. Jason Hart, Terry Hawrysh, Dr. Yoo-Joung Ko, Dr. Aly-Khan Lalani, Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Pierre Villeneuve, and Danica Wasney.

Meeting date: March 12, 2025

Regrets:

Five expert committee members did not attend.

Conflicts of interest:

None