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CADTH Reimbursement Recommendation

Daratumumab (Darzalex SC)

Indication: In combination with bortezomib, cyclophosphamide, and dexamethasone for the treatment of adult patients with newly diagnosed light chain (AL) amyloidosis

Sponsor: Janssen Inc.

Final recommendation: Reimburse with conditions

CADTH

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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

Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Darzalex?

CADTH recommends that Darzalex (daratumumab) in combination with cyclophosphamide, bortezomib, and dexamethasone (DCyBorD) should be reimbursed by public drug plans for the treatment of adult patients with newly diagnosed light chain (AL) amyloidosis if certain conditions are met.

Which Patients Are Eligible for Coverage?

Darzalex should only be covered to treat adult patients with newly diagnosed AL amyloidosis who have good performance status. Patients eligible for reimbursement of Darzalex must not have had prior therapy for AL amyloidosis or multiple myeloma, a previous or current diagnosis of multiple myeloma, or be planning to have a stem cell transplant during the first 6 cycles of treatment with DCyBorD.

What Are the Conditions for Reimbursement?

Darzalex should only be reimbursed if prescribed in combination with cyclophosphamide, bortezomib, and dexamethasone for 6 months, followed by daratumumab alone until the disease progresses or for a maximum of 2 years (whichever comes first), and if the cost of Darzalex is reduced.

Why Did CADTH Make This Recommendation?

- Evidence from a clinical trial demonstrated that DCyBorD was more effective than CyBorD alone in terms of hematologic and organ response outcomes in patients with newly diagnosed AL amyloidosis.
- Darzalex met patient needs for an effective treatment to maintain quality of life without debilitating side effects. DCyBorD is the only approved treatment option for AL amyloidosis in Canada.
- Based on public list prices, DCyBorD would not be considered cost-effective at a willingness to pay of $50,000 per quality-adjusted life-year (QALY). A price reduction of at least 21% is needed to ensure DCyBorD is cost-effective at a $50,000 per QALY threshold.
- Based on public list prices, the cost to participating drug plans is expected to be $94,917,168 over 3 years.

Additional Information

What Is AL Amyloidosis?

AL amyloidosis is a disease that occurs when an abnormal protein (amyloid) builds up in the organs, most commonly the heart and kidneys, and interferes with their normal function. AL amyloidosis is rare; in Canada, the annual incidence is 10 per million.

Unmet Needs in Darzalex

No treatments are currently publicly funded in Canada for patients with AL amyloidosis, and patients do not generally respond to those that are used. Therapies that can prevent, delay, or improve organ damage and are better tolerated by patients are needed.

How Much Does Darzalex Cost?

DCyBorD is given over a 28-day cycle. Treatment with DCyBorD is expected to cost public drug plans $31,892 per cycle in cycle 1 and cycle 2, $17,272 per cycle in cycle 3 to cycle 6, and $7,310 per cycle in subsequent cycles.

Recommendation

The CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) recommends that subcutaneous daratumumab in combination with cyclophosphamide, bortezomib, and dexamethasone (DCyBorD) be reimbursed for the treatment of adult patients with newly diagnosed light chain (AL) amyloidosis only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One open-label, phase III, randomized controlled trial demonstrated that treatment with DCyBorD resulted in clinically meaningful improvements in response outcomes for patients with newly diagnosed AL amyloidosis. The ANDROMEDA trial (N = 386) demonstrated that DCyBorD was associated with a higher hematologic complete response (CR) rate compared with cyclophosphamide, bortezomib, and dexamethasone (CyBorD) that was statistically significant (53.3% versus 18.1%; relative risk ratio = 2.9; 95% confidence interval [CI], 2.1 to 4.1, P < 0.001). The improvement in hematologic CR rate was consistent across patient subgroups of any cardiac stage and those with and without a t(11;14) translocation. The results for other response end points, including time to hematologic response and organ response (cardiac and renal), also favoured treatment with DCyBorD. The trial was powered to assess longer-term outcomes including major organ deterioration progression-free survival (MOD-PFS) — a composite end point comprising time to death, MOD, or hematologic progression — and overall survival (OS) but data on these end points were immature at the primary analysis. The assessment of health-related quality of life (HRQoL) was exploratory in the trial and had limitations that complicate interpretation of the data; however, the data suggested there was no detriment to patient HRQoL by adding daratumumab to CyBorD. The safety profile of DCyBorD was consistent with the known safety profile of daratumumab (i.e., neutropenia and infection) and the other individual components in the regimen, which were considered by pERC to be manageable.

AL amyloidosis is a rare and incurable disease that is associated with substantial morbidity and a poor prognosis. pERC agreed that there is a significant unmet need for effective publicly funded treatment options in this patient population. Patients identified a need for access to effective treatments that provide better quality of life without debilitating side effects so that they can carry out daily life activities. Given the totality of the evidence, pERC concluded that DCyBorD met some of these needs to a certain extent by providing an effective treatment that can prevent or delay side effects of the disease related to organ damage and maintain quality of life with manageable side effects.

Using the sponsor-submitted price for daratumumab and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for DCyBorD was $67,484 per quality-adjusted life-year (QALY) compared with CyBorD. At this ICER, DCyBorD is not cost-effective at a $50,000 per QALY willingness-to-pay threshold for adults with AL amyloidosis. A price reduction of at least 21% is required for DCyBorD to be considered cost-effective at a $50,000 per QALY threshold.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason
Initiation	
1. Treatment with DCyBorD should only be initiated in adult patients (≥ 18 years) with newly diagnosed AL amyloidosis who meet all of the following criteria: 1.1. histopathologic diagnosis of systemic AL amyloidosis based on detection by IHC and polarizing light microscopy of green birefringent in Congo red-stained tissue specimens or characteristic electron microscopy appearance 1.2. measurable disease by serum M protein ≥ 0.5 g/dL or abnormal serum free light chain ratio or a difference between involved and uninvolved free light chains (dFLC) ≥ 50 mg/L 1.3. involvement of at least 1 organ system 1.4. adequate hematologic, hepatic, and renal function (eGFR ≥ 20 mL/min/1.73 m^2).	Evidence from the ANDROMEDA trial demonstrated that treatment with DCyBorD had superior treatment efficacy in terms of hematologic and organ response outcomes in newly diagnosed patients with AL amyloidosis who had measurable disease and at least 1 involved organ at baseline.
2. Patients should have good performance status.	The ANDROMEDA trial enrolled patients with an ECOG performance status of ≤ 2. It is recognized that performance status may be related to underlying disease; therefore, for some patients, an improvement in status is expected after initiation of treatment. As such, clinicians could consider using DCyBorD in patients with an ECOG performance status > 2 at their discretion.
3. Patients must not have any of the following: 3.1. prior therapy for AL amyloidosis or multiple myeloma including medications that target CD38 3.2. previous or current diagnosis of multiple myeloma including the presence of lytic bone disease, plasmacytomas, ≥ 60% plasma cells in the bone marrow, or hypercalcemia 3.3. planned ASCT during the first 6 cycles of treatment.	No evidence was identified to demonstrate a treatment benefit of DCyBorD in patients who have had prior treatment for AL amyloidosis (with the exception of up to 160 mg of dexamethasone or equivalent corticosteroid) or those with a concurrent or prior diagnosis of multiple myeloma because these patients were excluded from the ANDROMEDA trial. Patients with Mayo Cardiac Stage IIIB or NYHA Classification IIIB or IV heart failure were excluded from the ANDROMEDA trial; however, pERC agreed with the clinical experts that these patients could be considered for treatment with DCyBorD at the discretion of the treating clinician.

Reimbursement condition	Reason
Discontinuation	
4. Treatment with daratumumab should be discontinued upon occurrence of any of the following: 4.1. evidence of hematologic progression or organ decompensation on treatment 4.2. unacceptable toxicity 4.3. renewal of daratumumab should be based on the absence of hematologic progression or organ function decompensation up to a maximum of 24 months.	In the ANDROMEDA trial, disease response and progression were assessed in accordance with the consensus guidelines for the conduct and reporting of clinical trials in systemic AL amyloidosis, and renal response and progression criteria by Palladini (2014). The maximum duration of treatment with daratumumab in the ANDROMEDA trial was 24 months. There is no evidence in support of a benefit of daratumumab beyond 24 months. In the ANDROMEDA trial, treatment with daratumumab was discontinued if patients completed the maximum duration of treatment, had unacceptable toxicity, or had confirmed hematologic progression or clinical manifestation of cardiac or renal failure.
5. Monitoring for hematologic response and progression should include the following: M protein, free light chains (serum and urine), cardiac biomarkers (NT-proBNP/BNP and troponin T), serum creatine, electrolytes, and alkaline phosphatase performed every month for the first 6 months of treatment, then every 3 months up to month 24.	In the ANDROMEDA trial, evaluations to assess hematologic response and progression were performed every 4 weeks during cycle 1 through cycle 6, and every 8 weeks from cycle 7 up to month 24 of treatment. In clinical practice, patients on daratumumab monotherapy would be monitored less frequently compared with the trial schedule. Based on clinical expert input, evaluations to assess hematologic response and progression on daratumumab monotherapy should be done every 3 months up to month 24.
Prescribing	
6. Daratumumab should be given in combination with CyBorD for 6 months followed by daratumumab monotherapy (starting in week 25) until disease progression or 24 cycles up to a maximum of 2 years.	No evidence was identified to support the efficacy of daratumumab when used in combination with any other regimens.
7. Daratumumab should be prescribed by a hematologist or oncologist with experience managing patients with amyloidosis or multiple myeloma in a cancer centre setting.	To ensure that daratumumab is prescribed only for appropriate patients and adverse effects are managed in an optimized and timely manner.
Pricing	
8. A reduction in price	The ICER for DCyBorD is $67,484 compared with CyBorD. A price reduction of at least 21% would be required for DCyBorD to be associated with an ICER of $50,000 per QALY compared with CyBorD. Because of uncertain evidence surrounding treatment duration and end-stage organ failure management costs, additional price reduction may be warranted.

AL = light chain; BNP = brain natriuretic peptide; ASCT = autologous stem cell transplant; CyBorD = cyclophosphamide plus bortezomib, and dexamethasone; DCyBorD = daratumumab plus cyclophosphamide, bortezomib, and dexamethasone; dFLC = difference between involved minus uninvolved serum free light chains; ECOG = Eastern Cooperative Oncology Group; eGFR = estimated glomerular filtration rate; ICER = incremental cost-effectiveness ratio; IHC = immunohistochemistry; NT-proBNP = N-terminal pro–brain natriuretic peptide; NYHA = New York Heart Association; pERC = CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee; QALY = quality-adjusted life-year.

Implementation Guidance

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

Table 2: Implementation Guidance From pERC

Condition no. in Table 1	Implementation considerations and guidance
3	For patients currently receiving CyBorD for AL amyloidosis who do not demonstrate a response to treatment, pERC agreed that daratumumab could be added to their CyBorD regimen. The timing of adding daratumumab to CyBorD should be left to the judgment of the treating clinician.

CyBorD = cyclophosphamide plus bortezomib, and dexamethasone; pERC = CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee.

Discussion Points

- pERC discussed that AL amyloidosis is a rare disease characterized by the deposition of light chain amyloid fibrils that accumulate predominantly in the heart and kidneys. pERC noted that cardiac damage is a major determinant of survival. Patients diagnosed at advanced stages, particularly when heart involvement is present, are at high risk of death within a few months.
- pERC discussed that DCyBorD is the first Health Canada–approved treatment for AL amyloidosis. CyBorD is considered the current standard of care for treatment in Canada; however, the regimen is used off-label and it is not funded in all jurisdictions. pERC noted that patients can currently access CyBorD through a special access program for a limited treatment duration. pERC agreed with clinicians and patients that there is a significant unmet need for effective publicly funded treatment options in this patient population who suffer substantial morbidity from their disease and have a poor prognosis.
- pERC discussed the results of the ANDROMEDA trial that demonstrated DCyBorD resulted in a significantly higher frequency of hematologic CR compared with CyBorD in patients with newly diagnosed AL amyloidosis. All secondary response outcomes, including organ response (cardiac and renal) and time to response, favoured treatment with DCyBorD. pERC considered these results as clinically meaningful considering clinician input that rapid response and organ responses are important goals of treatment because they signal prevention or delay of organ damage and correlate with OS. In the absence of mature data on longer-term outcomes (i.e., MOD-PFS and OS), pERC noted that the updated analysis of response outcomes based on a median follow-up of 20.3 months showed sustained benefit in patients treated with DCyBorD for hematologic CR and doubling rates of cardiac and renal response compared with CyBorD.
- Evidence from the ANDROMEDA trial suggested that HRQoL was similar in the 2 treatment groups during the first 6 cycles of treatment. After this point, patients in the DCyBorD arm reported continued improvement beyond cycle 6, which was observed across different HRQoL measures. However, pERC discussed that these results were based on an exploratory assessment, and there were other considerations that introduce uncertainty in the results, including longer duration of therapy and longer assessment of HRQoL in the DCyBorD group and the use of instruments, that may not capture the impact of specific

attributes of AL amyloidosis (i.e., organ and tissue impairment) on HRQoL. Based on the available evidence and clinician input that organ response in and of itself has positive impacts on patients' quality of life, pERC considered that there was no detriment to patients' HRQoL by adding daratumumab to CyBorD.

- pERC discussed that the safety profile of DCyBorD in the ANDROMEDA trial was consistent with the known safety profile of daratumumab (i.e., neutropenia and infection) and the other individual components in the regimen and agreed these are manageable in clinical practice. In the trial, the higher incidence of infections in the DCyBorD group rarely lead to treatment discontinuation or death. pERC noted that the incidence of certain cardiac adverse events (AEs) was higher in patients treated with DCyBorD; however, when treatment exposure was considered, exposure-adjusted rates of these AEs showed that cardiac toxicity in both treatment groups was primarily related to patients' underlying cardiomyopathy from AL amyloidosis.
- pERC discussed the uncertainty around end-stage organ failure management and the duration of treatment in the pharmacoeconomic analysis. This uncertainty suggests that the CADTH estimate of the necessary price reduction may be low, and a higher price reduction may be warranted.

Background

Daratumumab SC was approved by Health Canada in combination with CyBorD for the treatment of adult patients with newly diagnosed AL amyloidosis. Daratumumab is a human IgG1 kappa monoclonal antibody that binds CD38-expressing cells with high affinity. CD38 is a multifunctional glycoprotein ectoenzyme that is highly expressed on the cell surface of diverse hematologic malignancies including clonal plasma cells that produce the amyloidogenic immunoglobulin light chain. Daratumumab leads to the rapid and sustained elimination of highly immunosuppressive subsets of CD38+ cells. Daratumumab is supplied as an 1,800 mg/15 mL (120 mg/mL) solution for SC injection. The recommended dose is 1,800 mg administered subcutaneously over approximately 3 minutes to 5 minutes weekly (total of 8 doses) from week 1 to week 8, every 2 weeks (total of 8 doses) from week 9 to week 24, and every 4 weeks from week 25 onward until disease progression or 24 cycles up to a maximum of 2 years.

Sources of Information Used by the Committee

To make their recommendation, pERC considered the following information:

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

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

Stakeholder Perspectives

Patient Input

Myeloma Canada provided input for the review of daratumumab in combination with CyBorD for the treatment of AL amyloidosis. Myeloma Canada conducted a survey in their patient and caregiver community via email and social media. The survey was available from July 12 to July 25, 2021. The survey received 40 responses, 12 of which were deemed eligible (from 7 patients currently receiving CyBorD, 3 patients currently receiving DCyBorD, and 2 patients waiting to receive treatment). All patients surveyed rated access to effective treatments for AL amyloidosis as extremely important. The respondents who had treatment experience with CyBorD (n = 7) indicated that before taking CyBorD their expectations of a new treatment were "minimal side effects," which was mentioned by most patients (n = 4), followed by "disease control" (n = 3) and "improved quality of life" (n = 1). All patients treated with CyBorD rated their experience with this treatment regimen as "somewhat tolerable," "tolerable," or "very tolerable." Fatigue and neuropathy were cited as the least tolerable side effects of CyBorD. Patients who had been treated with combined daratumumab and CyBorD rated their overall side effects as "somewhat tolerable," "tolerable," or "very tolerable." One patient found the side effects of bortezomib and cyclophosphamide intolerable; 1 patient was treated with daratumumab and dexamethasone only. In terms of what is important to patients when it comes to treating their AL amyloidosis, the majority of patient responses described a strong desire for effective treatments, a good or better quality of life, and being able to continue daily activities without debilitating side effects of treatment.

Clinician Input

Input From Clinical Experts Consulted by CADTH

The clinical expert consulted by CADTH noted that no treatments other than DCyBorD are currently approved or generally funded for the treatment of AL amyloidosis in Canada. CyBorD is used off-label and may be accessed through the manufacturer's special access program for a limited treatment duration and, in some provinces (e.g., Alberta), it is funded based on a special agreement with provincial groups. DCyBorD is amenable to use for most patients with newly diagnosed AL amyloidosis. In terms of response assessment, the clinical expert noted that improved hematologic response, PFS, OS, as well as organ response and HRQoL can be considered clinically meaningful responses to treatment. With respect to frequency of assessment of treatment response, the clinical expert indicated that monthly assessments are common in Canada but decisions on adequate hematologic and organ responses are made after 3 months and 6 months from initiation of treatment. The clinical expert indicated that daratumumab is a practice-changing regimen in a disease area where no approved or funded treatments exist.

Clinician Group Input

Clinician input was received from the CMRG and the Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee. The clinician group noted that the most important goals of any plasma cell–directed therapy is to achieve deep and rapid responses in terms of eliminating the clonal plasma cells and hence the monoclonal protein product it secretes. Based on the data from the ANDROMEDA trial's control arm, the deep responses necessary for the organ improvement and prolonged disease control are not optimal with CyBorD alone. Given the toxic effect of the amyloid light chain, it is vital to achieve rapid and deep responses and to have access to therapies in the first line that produce deep and quick responses. The clinician group noted that DCyBorD is a major breakthrough in AL amyloidosis, which, if not treated quickly and with deep responses, can lead to irreversible organ damage. Based on encouraging results of the ANDROMEDA trial, fewer AL patients may require ASCT, with its attendant risk of morbidity and increased mortality in this disease, if DCyBorD is approved for this indication. The clinician group also noted that DCyBorD is well-tolerated with SC dosing of both daratumumab and bortezomib and produces minimal hematologic toxicity, therefore almost all newly diagnosed AL patients would be potential candidates. The rapid responses it can generate can be associated with rapid organ improvement. The clinician group also noted that an important consideration — and a particular concern for CMRG physicians — is the lack of access to daratumumab regimens for the current population of Canadian patients with AL amyloidosis who have already received first-line therapy and for whom daratumumab at relapse could be life-saving or life-extending. Although this is expected be a limited group of patients, the clinician group believes that these patients deserve the chance to receive daratumumab therapy at disease progression, because of the limited range of other options.

Drug Program Input

The drug programs identified jurisdictional implementation issues related to considerations for initiation and prescribing of therapy and generalizability. pERC weighed evidence from the ANDROMEDA trial and other clinical considerations, including input from the clinical experts consulted by CADTH, to provide responses to the drug programs' implementation questions, which are presented in Table 3.

Table 3: Responses to Questions From the Drug Programs

Implementation issues	Response
Considerations for initiation of therapy	
Only a small proportion of patients in the ANDROMEDA trial proceeded to ASCT (6.7% in the DCyBorD group and 10.6% in the CyBorD group). Please confirm that patients who proceed to ASCT are not eligible for daratumumab maintenance therapy post-ASCT?	pERC agreed that patients who undergo ASCT after receiving DCyBorD would not be eligible for daratumumab maintenance therapy post-ASCT.
Would patients who complete 2 years of daratumumab maintenance therapy and subsequently relapse be eligible for re-treatment with DCyBorD followed by daratumumab maintenance? If so, what is the appropriate interval for re-treatment?	The ANDROMEDA trial is ongoing, therefore there is currently no evidence from the trial to inform on re-treatment with DCyBorD and daratumumab maintenance at relapse.

Implementation issues	Response
Would patients who complete up to 6 cycles of DCyBorD, followed by ASCT be eligible for re-treatment with DCyBorD and daratumumab maintenance? If so, what is the appropriate interval for re-treatment?	pERC agreed with the clinical experts that if a deep response is achieved with DCyBorD, patients may not require ASCT. As previously noted, there is currently no evidence from the trial to inform on re-treatment with DCyBorD and daratumumab maintenance at relapse.
Considerations for prescribing of therapy	
For patients unable to tolerate the SC formulation, would an IV equivalent dosing (16 mg/kg IV) for daratumumab be appropriate?	pERC agreed with the clinical experts that daratumumab can be administered by IV when SC administration is not possible or contraindicated.
Additional comments: • The comparator in the ANDROMEDA trial was CyBorD, which is standard of care in all provinces. It was noted that there is some variation in dosing of bortezomib and duration of therapy. • Funding may vary across provinces. Drugs used in the treatment of AL amyloidosis may fall outside of the cancer drug budget in some jurisdictions. • Variation in dosing frequency of daratumumab containing regimens could potentially lead to errors. • Red blood cell genotyping is recommended before the initiation of therapy. • A large budget impact of a relatively small number of patients is expected. • Generic bortezomib is available.	pERC acknowledged these issues raised by the drug plans.
Generalizability	
Please confirm that patients with advanced cardiac disease (Mayo Stage IIIB or NYHA Class IIIB or IV) would not be eligible for DCyBorD?	pERC agreed with the clinical experts that treatment with DCyBorD should not be limited by cardiac stage and that patients with advanced cardiac disease (e.g., Mayo Stage IIIB or NYHA Classification IIIB or IV) should be eligible for DCyBorD at the discretion of the treating physician. If patients are suitable for CyBorD treatment, the addition of daratumumab is expected to lead to better response without causing significant toxicity.
On a time-limited basis, should patients currently on CyBorD (or another regimen) whose disease has not yet progressed be switched over to DCyBorD? If yes, is there an appropriate time frame based on the number of cycles? On a time-limited basis, should patients who recently completed CyBorD, but whose disease has not yet progressed, be eligible for daratumumab maintenance? If yes, is there an appropriate time frame?	pERC agreed with the clinical experts that if a patient on CyBorD progresses or shows no response from initiation of treatment, they can have daratumumab added to their regimen. The timing of adding daratumumab to CyBorD should be left to the judgment of the treating clinician. Patients who achieve an adequate response on CyBorD do not need to be treated with daratumumab as maintenance therapy.

ASCT = autologous stem cell transplant; CyBorD = cyclophosphamide plus bortezomib, and dexamethasone; DCyBorD = daratumumab plus cyclophosphamide, bortezomib, and dexamethasone; NYHA = New York Heart Association; pERC = CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee.

Clinical Evidence

Pivotal Studies and Protocol-Selected Studies

Description of Studies

The ANDROMEDA trial is an ongoing, randomized, open-label, active-controlled, phase III, multi-centre trial designed to compare the efficacy of DCyBorD to CyBorD alone in the treatment of patients with newly diagnosed AL amyloidosis. Patients were stratified by cardiac stage based on the Mayo Clinical Cardiac Staging System (stages I, II, and IIIa), ASCT availability in the country of residence, and renal function (creatinine clearance ≥ 60 mL/min or < 60 mL/min) and were randomly assigned in a 1:1 ratio to receive either DCyBorD or CyBorD. The primary end point was a hematological CR in the intention-to-treat population. The key secondary efficacy end points were MOD-PFS, organ response rate, OS, overall hematologic response (CR, very good partial response, or partial response), and time and duration of hematologic response. HRQoL and medical resource utilization were also evaluated as exploratory end points.

A total of 388 patients were randomized to treatment with either DCyBorD (n = 195) or CyBorD (n = 193). The median age in the study population was 64 years (62 years and 64 years in the DCyBorD and CyBorD treatment arms, respectively). The median number of organs involved at baseline was 2 (range = 1 to 6) and 65.5% of patients had 2 or more organs involved. Cardiac and renal involvement were most common, affecting 71.4% and 59.0% of patients in the DCyBorD and CyBorD treatment arms, respectively. Approximately one-third (36.6%) of patients were cardiac stage III at baseline. Of the 202 patients tested for t(11;14) at baseline, 106 had t(11;14) present (DCyBorD: 51patients; CyBorD: 55 patients).

Efficacy Results

At the primary analysis (data cut-off date: 14 February 2020; median follow-up of 11.4 months), 104 (53.3%) patients in the DCyBorD arm and 35 (18.1%) in the CyBorD arm had an independent review committee–assessed hematologic CR (relative risk ratio = 2.9; 95% CI, 2.1 to 4.1, P < 0.001).

Hematologic CR rates across cardiac stages were consistent with the results observed in the overall population of patients. The hematologic CR rate was higher in the DCyBorD arm compared with the CyBorD arm for all cardiac stages. The difference between hematologic CR rates in the 2 treatment arms increased by Mayo Cardiac Stage (DCyBorD versus CyBorD: 45% versus 28% for cardiac stage I; 54% versus 20% for stage II and 58% versus 10% for stage III, respectively). Similarly, the magnitude of hematologic CR rates in the t(11;14) translocation subgroup was similar to that observed in the overall population. Patients in the DCyBorD arm had equally high rates of hematologic CR regardless of t(11;14) translocation, whereas lower hematologic CR rates were observed for patients with the t(11;14) translocation treated with CyBorD.

Among the responders, the median time to hematologic CR was 60 (range = 8 to 299) days in the DCyBorD arm and 85 (range = 14 to 340) days in the CyBorD arm. At the time of the primary analysis, the median duration of hematological CR had not been reached in either treatment arm (range = 0.85 to 17.5 months for DCyBorD; 0.03 to 18.4 months for CyBorD). Of the 104 patients who achieved hematological CR in the DCyBorD arm, 4 patients died while in hematological CR and no patients relapsed following hematological CR. Of the 35 patients who achieved hematological CR in the CyBorD arm, 2 patients died while in hematological

CR and 2 patients relapsed following hematological CR. The hazard ratio for MOD-PFS for DCyBorD versus CyBorD was 0.58 (95% CI, 0.36 to 0.93).

For patients who could be evaluated for cardiac response, 41.5% of patients in the DCyBorD arm and 22.2% of patients in the CyBorD arm had a cardiac response at 6 months. Among patients who could be evaluated for renal response, 53.0% of patients in the DCyBorD arm and 23.9% of patients in the CyBorD arm had a renal response at 6 months. In the updated analysis, the 12-month organ response rate for cardiac response in the DCyBorD arm and CyBorD arm was 57% and 28%, respectively; for renal response, it was 57% and 27%, respectively.

Median OS was not reached in either treatment arm.

Patient Reported Outcomes

The median time to improvement for global health status as measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) was 7.8 months in the DCyBorD arm and 16.7 months in the CyBorD arm (hazard ratio = 1.53, 95% CI, 1.10 to 2.13). EORTC QLQ-30 global health status showed continued improvement in the DCyBorD arm after 6 months when patients were receiving daratumumab monotherapy.

Medical resource utilization was reported for [redacted] and [redacted] of patients in the DCyBorD and CyBorD arms, respectively. Use [redacted]. The most common indication for use of medical services was [redacted] arm.

Harms Results

Nearly all patients experienced at least 1 treatment-emergent AE (TEAE) (DCyBorD: 97.9%; CyBorD: 98.4%). In both treatment arms, TEAEs led to discontinuation of study treatment in approximately 4% of patients. A higher percentage of patients (43.0%) in the DCyBorD arm reported at least 1 serious TEAE compared with the CyBorD arm (36.2%). The most commonly reported (≥ 5% in either treatment arm) serious AEs were pneumonia (DCyBorD: 7.3%, CyBorD: 4.8%) and cardiac failure (DCyBorD: 6.2%, CyBorD: 4.8%). The incidence of was a minimum of 2% higher in the DCyBorD arm compared with the CyBorD arm for pneumonia (7.3% and 4.8%, respectively), sepsis (3.1% and 0%, respectively), and cardiac arrest (3.6% and 1.6%, respectively).

Across all cycles, the incidence of any grade of neutropenia (DCyBorD: 10.9%; CyBorD: 6.4%) and Grade 3 or 4 neutropenia (DCyBorD: 5.2%; CyBorD: 2.7%) was higher in the DCyBorD arm. The incidence of any grade of infection (DCyBorD: 65.8%; CyBorD: 53.7%), Grade 3 or 4 of infection (DCyBorD: 16.6%; CyBorD: 10.1%), and serious infection (DCyBorD:16.1%; CyBorD: 8.5%) was higher in the DCyBorD arm. The most commonly reported (> 10% in either treatment arm) infections (any grade) in the DCyBorD and CyBorD arms were upper respiratory tract infection (25.9% and 11.2%, respectively) and pneumonia (10.9% and 6.4%, respectively).

At the time of the primary analysis, 27 (14.0%) patients in the DCyBorD arm and 28 (14.9%) patients in the CyBorD arm died. One patient in the CyBorD arm died before receiving any treatment. A higher proportion of patients in the DCyBorD arm reported death due to an AE (11.9%) compared with the CyBorD arm (7.4%), and more patients in the CyBorD arm

compared with the DCyBorD arm reported death due to progressive disease (1.0% and 4.8%, respectively) and "other" causes (1.0% and 2.7%, respectively). The most common (≥ 2% in either treatment arm) AEs leading to death in the DCyBorD and CyBorD arms were cardiac disorders: cardiac arrest (3.1%and 1.6%, respectively), sudden death (3.1% and 1.6%, respectively), and cardiac failure (2.6% and 0.5%, respectively). All patients who died due to cardiac disorders had cardiac involvement at baseline (DCyBorD: 14 of 14; CyBorD: 7 of 7).

Critical Appraisal

The ANDROMEDA trial was an open-label study; patients and investigators were not blinded to study assignment, although patient blinding would not have been possible given the differences in the 2 study treatment regimens. Nonetheless, sources of bias that may result from lack of blinding of patients and investigators to assigned study treatments cannot be ruled out. For example, a patient's knowledge of their assigned treatment may have affected some safety end points and particularly HRQoL, and different concomitant supportive care may have been offered to patients in the 2 treatment arms. The primary end point of hematologic CR and organ response were lab-based objective measures, which were unlikely to be affected by the open-label design. Longer duration of therapy in the DCyBorD arm and use of subsequent therapy in the trial is another possible source of bias. Only the primary outcome of hematologic CR is unaffected by this possible bias and can thus be considered valid. Use of subsequent therapy may impact other key secondary outcomes: very good partial response, partial response, and MOD-PFS. This issue is addressed in the primary analysis for MOD-PFS which employed the inverse probability of censoring weight method to adjust estimates of a treatment effect in the presence of subsequent non–cross-resistant, anti-plasma cell therapy, which still showed longer MOD-PFS in the DCyBorD arm. Missing data, including missing organ response assessments and patient attrition (26.6% in the DCyBorD and 35.2% in the CyBorD arm), although not unexpectedly high in the cancer trial setting, may also impact the internal validity of the evidence.

Although the ANDROMEDA trial included a heterogenous population of patients with AL amyloidosis and a wide range of clinical presentations were well-represented, some groups of patients, including those with an advanced cardiac stage, were excluded. Therefore, the evidence regarding efficacy and safety of DCyBorD compared with CyBorD in these groups of patients is limited based on trial evidence. The comparator of the trial (CyBorD) is not approved for treatment of patients with AL amyloidosis in Canada. However, CyBorD is an appropriate comparator because it is standard of care for newly diagnosed AL amyloidosis in Canada. This is a special instance in which the drug regimen under review (i.e., DCyBorD) is the only Health Canada–approved treatment. The primary and key secondary outcomes and the assessment schedule were also reflective of clinical practice. Based on input from the clinical expert consulted by CADTH and clinician groups, in clinical practice, patients are assessed every 3 to 6 months. Formal response criteria have been established previously and were included in the ANDROMEDA trial.

Economic Evidence

Table 4: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Decision tree followed by Markov model
Target population	Adult patients with newly diagnosed AL amyloidosis
Treatments	DCyBorD
Submitted price	Daratumumab SC: $7,310 per 1,800 mg vial
Treatment cost	Recommended dosage: • Cycle 1 and cycle 2: 1,800 mg 4 times per 28 days • Cycle 3 to cycle 6: 1,800 mg twice per 28 days • ≥ Cycle 7: 1,800 mg once per 28 days $31,892 for cycles 1 to 2, $17,272 for cycles 3 to 6, $7,310 for cycles ≥ 7
Comparators	CyBorD
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (35 years)
Key data source	• An open-label, phase III trial (ANDROMEDA) comparing DCyBorD with CyBorD in adults with newly diagnosed AL amyloidosis was used to stratify patients based on their hematologic response as part of a decision tree, and to assign transition probabilities, health state utilities, and frequency of adverse events in the Markov model • A retrospective study from Greece (Kastritis et al. [2020]) was used to estimate the overall survival associated with different hematologic responses
Key limitations	• The sponsor made several assumptions while deriving the transition probabilities, costs, and utilities associated with end-stage organ failure which are not all aligned with one another and may be biased in favour of DCyBorD. • The model's estimates of long-term survival were derived from a retrospective cohort study, which contributes meaningful uncertainty that could not be addressed through reanalysis. • The use of a RDI potentially underestimates drug costs because RDI includes dose delays, reductions, escalations, and other factors which may not correlate directly with drug costs. Furthermore, there is uncertainty surrounding how wastage considerations might affect the calculation of RDI. • The duration of treatment may be underestimated, which creates an estimate of drug acquisition cost that favours DCyBorD.

Component	Description
CADTH reanalysis results	• CADTH made 1 change to the base case which involved assuming 100% RDI for all comparators. • Based on the CADTH base case, DCyBorD was associated with an ICER of $67,484 per QALY, and the probability of cost-effectiveness at a $50,000 per QALY threshold was 31.6%. A price reduction of 21% would be required to achieve cost-effectiveness at this threshold. • Scenario analyses were performed to assess other aspects of uncertainty surrounding treatment duration, proportion of patients on hemodialysis, utility of end-stage disease, OS extrapolation, and pharmacy dispensing fees. The scenario involving maximum treatment duration resulted in an ICER of $88,004 per QALY and the scenario assuming half of patients in end-stage renal disease that would require hemodialysis resulted in an ICER of $80,954 per QALY.

CyBorD = cyclophosphamide plus bortezomib, and dexamethasone; DCyBorD = daratumumab plus cyclophosphamide, bortezomib, and dexamethasone; ICER = incremental cost-effectiveness ratio; LY = life-year; RDI = relative dose intensity; QALY = quality-adjusted life-year; SC = subcutaneous.

Budget Impact

CADTH reanalysis fixed the derivation of the population size along with a small programming inconsistency. In the CADTH base case, the budget impact is expected to be $25,887,024 in year 1, $34,273,444 in year 2, and $34,756,670 in year 3, with a 3-year total of $94,917,168.

pERC Information

Members of the Committee

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Matthew Cheung; Dr. Winson Cheung, Dr. Michael Crump, Dr. Leela John, Dr. Christian Kollmannsberger, Mr. Cameron Lane, Dr. Christopher Longo, Dr. Catherine Moltzan, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

Meeting date: December 1, 2021

Regrets: None

Conflicts of interest: None