pCODR EXPERT REVIEW COMMITTEE (pERC)
INITIAL RECOMMENDATION

The CADTH pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug reimbursement decisions. The pCODR process brings consistency and clarity to the assessment of cancer drugs by looking at clinical evidence, cost-effectiveness, and patient perspectives.

Providing Feedback on This Initial Recommendation
Taking into consideration feedback from eligible stakeholders, the pCODR Expert Review Committee (pERC) will make a Final Recommendation. Feedback must be provided in accordance with *pCODR Procedures*, which are available on the pCODR website. The Final Recommendation will be posted on the pCODR website once available, and will supersede this Initial Recommendation.

Drug:
Brentuximab vedotin (Adcetris)

Submitted Funding Request:
Brentuximab vedotin (BV) is indicated for the post-autologous stem cell transplant (ASCT) consolidation treatment of patients with Hodgkin lymphoma (HL) at increased risk* of relapse or progression.

*The definition of increased risk of post-ASCT relapse or progression is based on the AETHERA trial: refractory to frontline therapy, relapsed less than 12 months following frontline therapy, or relapse at greater or equal to 12 months with extranodal involvement.

Submitted by:
Seattle Genetics, Inc.

Manufactured by:
Seattle Genetics, Inc.

NOC Date:
July 20, 2017

Submission Date:
August 10, 2017

Initial Recommendation Issued:
February 1, 2018

Approximate Per-Patient Drug Costs, Per Month (28 Days)

Submitted list price
Brentuximab vedotin: $4,840.00 per 50 mg vial

Note: Costs are calculated based on an average weight of 70 kg and body surface area of 1.7m².

Brentuximab vedotin costs:

- $19,360.00 per 28-day course

pERC RECOMMENDATION

pERC recommends reimbursement of brentuximab vedotin (BV) for the post-autologous stem cell transplant (ASCT) consolidation treatment of patients with Hodgkin lymphoma (HL) at increased risk (see *Definition of Increased Risk* on page 2) of relapse or progression, conditional on cost-effectiveness being improved to an acceptable level. BV consolidation treatment should be initiated within four to six weeks post-ASCT or upon recovery from ASCT and continued until a maximum of 16 cycles, disease progression, or unacceptable toxicity, whichever comes first.

The Committee made this recommendation because it was satisfied that there is a net clinical benefit of BV consolidation therapy compared with placebo, based on a statistically significant and clinically meaningful improvement in progression-free survival (PFS), no

significant decrement in quality of life (QoL), a manageable toxicity profile, and a need for treatment options in this small population of patients who are at increased risk for disease progression or relapse post-ASCT.

pERC was also satisfied that BV aligns with patient values, in that it offers a treatment option with the opportunity to maintain disease control, and has manageable side effects.

The Committee concluded that BV consolidation therapy, at the submitted price and given the uncertainly in the magnitude of long-term overall survival benefit, is not cost-effective compared with placebo. pERC also highlighted that the submitted budget impact of BV consolidation therapy is likely underestimated and may be substantially higher, given that the market uptake may be greater than estimated.

Definition of Increased Risk
pERC noted that the definition of increased risk of post-ASCT relapse or progression is based on the AETHERA trial: refractory to frontline therapy, relapsed less than 12 months following frontline therapy, or relapse at greater or equal to 12 months with extranodal involvement.

POTENTIAL NEXT STEPS FOR STAKEHOLDERS

Generalizability of Results to Patients With Other High-Hisk Factors
pERC discussed that there is currently insufficient evidence to make an informed recommendation on the use of BV consolidation therapy in high-risk patient subgroups, other than those defined in the trial. However, pERC agreed that there is no biological rationale to assume that outcomes of BV consolidation therapy would be any less effective or significantly more toxic in patients with risk factors other than those defined in the AETHERA trial. pERC suggested that jurisdictions may want to develop a national consensus on a possible broader definition of increased risk. Additional high-risk features may include: B symptoms, less than a complete response to salvage therapy as assessed by computed tomography (CT) or positron emission tomography (PET) scan, relapse in a prior radiation field, or the requirement of more than one line of salvage therapy pre-ASCT.

Pricing Arrangements to Improve Cost-Effectiveness and Reduce the Budget Impact
Given that pERC was satisfied that there is a net clinical benefit of BV for the post-ASCT consolidation treatment of patients with HL at increased risk of relapse or progression, jurisdictions may want to consider pricing arrangements that would improve the cost-effectiveness of BV to an acceptable level as well as reduce the potential budget impact. pERC noted that a substantial reduction in the price of BV would be required to improve the cost-effectiveness and reduce the budget impact to acceptable levels.

Factors Affecting Budget Impact and Adoption Feasibility
pERC noted that the submitted budget impact analysis (BIA) was most sensitive to the following changes: (1) assuming a higher market uptake, (2) assuming a longer treatment duration, and (3) increasing the number of HL patients assumed to relapse or to be refractory after frontline therapy. pERC discussed that, if BV consolidation therapy were implemented, the market uptake of BV consolidation therapy could be much higher than estimated by the submitter's BIA, given that health care professionals are already familiar with its administration in other indications and that adverse events are

manageable. The Committee agreed that the BIA is substantially underestimated.

Available Vial Size and Wastage
pERC noted the high cost and potential for drug wastage associated with BV consolidation therapy. BV is priced per vial, and there are only 50 mg vials available. pERC noted that BV has 24-hour stability after reconstitution and vial sharing may be unlikely, because of the small patient population. pERC agreed that jurisdictions will need to consider mechanisms to minimize wastage upon implementation of a reimbursement recommendation, including advocating for the availability of a smaller vial size.

Re-Treatment with Brentuximab Vedotin
There is currently insufficient evidence to make an informed recommendation on re-treatment with BV. pERC noted that re-treatment of patients with BV who (1) have received and responded to BV pre-ASCT, or (2) have relapsed after receiving BV consolidation therapy post-ASCT, is out of scope of this review. pERC agreed with the CGP's speculation that, rather than re-treatment with BV, clinicians might move to other options, such as PD-1 inhibitors.

Optimal Timing of BV (Consolidation Therapy Versus Treatment After Progression)
pERC noted that the overall survival analysis in the AETHERA trial was immature and confounded by the high cross-over rate of patients in the placebo group to BV. Importantly, this precluded a conclusion on the optimal timing of brentuximab (that is, as consolidation therapy or as treatment after progression). pERC noted that availability of BV as consolidation therapy in the post-ASCT setting may reduce the number of recurrences and hence the need for BV therapy for relapsed disease post-ASCT. pERC noted that the treatment goal of BV consolidation therapy is with curative intent, whereas the treatment goal of BV after failure of ASCT is with palliative intent only.

Please note: Provincial Advisory Group (PAG) questions are addressed in detail in the Summary of pERC Deliberations and in a summary table in Appendix 1.

SUMMARY OF pERC DELIBERATIONS

Hodgkin lymphoma (HL) is an uncommon but distinct lymphoma subtype that has a bimodal age distribution. It is seen in both children and adolescents and in adults more than 60 years of age. HL accounts for approximately 8-10% of all diagnoses of lymphoma. The median age at diagnosis in most reported series is 35-40 years and approximately 15% of patients are older than 60 years. There are approximately 900 new cases of HL in Canada each year and approximately 160 Canadians will die annually from this disease. While the majority of patients with HL are cured with initial therapy, up to 30% of patients with advanced stage disease (Ann Arbor stage 3 and 4) and 10-15% with limited disease will experience disease progression during or relapse after primary therapy. Patients who experience treatment failure (disease progression on or relapse after primary therapy) are usually candidates for second-line (sometimes called salvage) chemotherapy followed by high-dose chemotherapy supported by autologous stem cell transplantation (ASCT). Second-line treatment including ASCT cures approximately 50% of patients. Patients who experience relapse after ASCT have very limited treatment alternatives and are generally treated with palliative intent. There is currently no known therapy to improve progression-free or overall survival for patients at increased risk of disease recurrence following ASCT. The pCODR Clinical Guidance Panel (CGP) agreed with the registered clinicians that observation with best supportive care (BSC) is the only current approach in this setting. pERC concluded that there is a significant unmet need for treatments that prolong remission and potentially cure patients with HL at increased risk for progression/ relapse post-ASCT.

pERC's *Deliberative Framework* for drug reimbursement recommendations focuses on four main criteria:	
CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

pERC deliberated on the results of one phase III, double-blind, randomized controlled trial (AETHERA), that evaluated the efficacy and safety of brentuximab vedotin (BV) consolidation therapy and BSC compared with placebo plus BSC in patients with HL at increased risk for disease progression or relapse. pERC considered that the progression-free survival (PFS) results (as assessed by independent review) were statistically significant and clinically meaningful in favour of BV consolidation therapy. pERC discussed that the results for overall survival (OS) (a secondary outcome) were not yet mature and may be confounded, even with sufficient follow-up, as patients were permitted to receive subsequent anti-cancer therapies including BV upon disease progression. In the absence of OS data, pERC discussed the clinical meaningfulness of PFS in the setting of consolidation therapy post-ASCT. pERC agreed with the CGP as well as with the input from registered clinicians that the use of ASCT in relapsed or refractory HL has curative intent, and the purpose of adjuvant BV consolidation therapy post-ASCT is to support that goal. pERC noted that upon relapse, post-ASCT treatment options have palliative intent only. Therefore, the Committee concluded that the PFS benefit observed in AETHERA was statistically significant and clinically meaningful.

pERC deliberated on the toxicity profile of BV consolidation therapy and noted there were more frequent toxicities compared with placebo. Neutropenia, peripheral sensory neuropathy, thrombocytopenia, and peripheral motor neuropathy were the most common adverse events. While peripheral neuropathy was the main reason for treatment delay or discontinuation, it generally resolved or improved within 12 to 16 weeks of stopping BV consolidation therapy. Overall, pERC agreed with the CGP that BV can be given safely as consolidation therapy and toxicities can be mitigated with careful dose modification and/or dose delay.

pERC discussed the available patient-reported outcomes data from the AETHERA trial. pERC noted that in both treatment groups, EuroQoL 5-Dimensions (EQ-5D) utility index scores worsened over time with slightly worse scores observed in the BV group compared with placebo. However, pERC noted that the mean differences in index scores between treatment groups did not exceed the minimal clinically important difference (MCID), except during the post-treatment phase at months 15 and 18. Furthermore, pERC noted that the decrease in quality of life (QoL) compared with baseline was not associated with treatment-emergent peripheral neuropathy at any time point. pERC noted that an improvement in QoL in this post-ASCT population in remission or with active lymphoma would be unlikely. The Committee concluded that the AETHERA data did not show a negative effect of BV consolidation therapy on QoL

compared with placebo, which pERC considered to be reasonable in the setting of consolidation treatment.

pERC concluded that there is a net clinical benefit to BV consolidation therapy, compared with placebo, in the treatment of patients with HL at increased risk for disease progression post-ASCT. In making this conclusion, pERC considered the clinically meaningful results in PFS, a modest decrement in QoL, a manageable toxicity profile, and an unmet need for treatment options in this small population of patients with HL at increased risk for disease progression/ relapse post-ASCT.

pERC reviewed patient advocacy group input and concluded that BV consolidation therapy aligns with patient values. pERC noted that according to patient group input, HL manifests as stressful disease symptoms, such as fatigue or lack of energy, enlarged lymph nodes, drenching night sweats, itching, persistent cough, and mental/emotional problems such as anxiety and difficulties with concentrating. Patients reported that, overall, BV consolidation therapy had positively affected their health and well-being, despite several side effects, with peripheral neuropathy being one of the more significant concerns. Notably, as reported by the patients providing input, BV had a positive impact on the ability to work and attend school, spend time with family and participate in activities, or travel. pERC agreed that BV consolidation therapy offers a treatment option with the opportunity to maintain disease control, and has manageable side effects. As a result, the Committee concluded that BV consolidation therapy aligned with patient values.

pERC deliberated on the cost-effectiveness of BV consolidation therapy in patients with HL at increased risk for progression/ relapse post-ASCT and concluded that BV consolidation therapy is not cost-effective when compared with BSC at the submitted price. pERC noted that the submitted base-case the incremental cost-effectiveness ratio (ICER) was lower than the pCODR Economic Guidance Panel's (EGP's) lower and upper bound ICER. The Committee noted several limitations in the submitted analysis, particularly the lack of OS data from the AETHERA trial and the resulting uncertainty in the estimates of the ICER. pERC noted that in the absence of OS data, the model used PFS data as a proxy for overall survival. Long-term survival was derived from a modelled extrapolation of the Kaplan–Meier PFS curves. pERC agreed with the EGP that this structural limitation increased the uncertainty in the incremental cost-effectiveness. Furthermore, the Committee noted that the EGP made the following changes to the model to address some of its limitations: (1) use of independently-assessed instead of investigator-assessed PFS outcomes, (2) a shorter time horizon to address the uncertainty in survival estimates based on extrapolation of short-term trial data, and (3) a longer treatment duration as the CGP indicated that patients would not discontinue treatment due to toxicity. Overall, pERC agreed with the EGP's reanalysis and the limitations identified in the submitted economic model. Therefore, pERC accepted the EGP's ICER estimates. Consequently, pERC concluded that BV consolidation therapy was not cost-effective at the submitted price compared with BSC.

pERC discussed the feasibility of implementing a reimbursement recommendation for BV consolidation therapy in patients with HL at increased risk for progression/ relapse post-ASCT. pERC discussed that, if BV consolidation therapy were implemented, the market uptake of BV consolidation therapy could be much higher than estimated by the submitter's budget impact analysis (BIA) given that health care professionals are already familiar with its administration in other indications and that adverse events are manageable. pERC acknowledged that, according to the EGP's reanalysis, the submitted BIA was most sensitive to the following changes: (1) assuming a higher market uptake, (2) a longer treatment duration, and (3) increasing the number of HL patients assumed to relapse or to be refractory after frontline therapy. The Committee agreed that jurisdictions will need to consider the uncertainty in these factors upon implementation, and that the BIA is substantially underestimated.

pERC noted the high cost and potential for drug wastage associated with BV consolidation therapy. BV is priced per vial, and there are only 50 mg vials available. pERC noted that BV has 24-hour stability after reconstitution and vial sharing may be unlikely. pERC agreed that jurisdictions will need to consider mechanisms to minimize wastage upon implementation of a reimbursement recommendation, including advocating for the availability of a smaller vial size.

pERC discussed the Provincial Advisory Group's (PAG's) request for guidance on a number of clinical scenarios to assist with implementation. PERC discussed that there is currently insufficient evidence to make an informed recommendation on the use of BV consolidation therapy in high-risk patient subgroups, other than those defined in the trial. However, pERC also noted that there is no biological rationale to assume that outcomes of BV consolation therapy would be different in patients with risk factors other than those defined in the AETHERA trial. pERC suggested that jurisdictions may want to develop a

national consensus on a possible broader definition of increased risk. Additional high-risk features may include: B symptoms, less than a complete response to salvage therapy as assessed by CT or PET scan, relapse in a prior radiation field, or the requirement of more than one line of salvage therapy pre-ASCT.

pERC discussed that there is currently insufficient evidence to make an informed recommendation on the use of BV consolidation therapy in patients without the high-risk features that defined AETHERA study eligibility; that is, patients who relapse >12 months post-ASCT, and without extranodal disease.

Further, pERC noted that there is currently insufficient evidence to make an informed recommendation on re-treatment with BV. pERC noted that re-treatment of patients with BV who (1) have received and responded to BV pre-ASCT, or (2) have relapsed after receiving BV consolidation therapy post-ASCT, is out of scope of this review. pERC agreed with the CGP's speculation that, rather than re-treatment with BV, clinicians might move to other options, such as PD-1 inhibitors.

pERC noted that the overall survival analysis in the AETHERA trial was immature and confounded by the high cross-over rate of patients in the placebo group to BV. Importantly, this precluded a conclusion on the optimal timing of brentuximab (that is, as consolidation therapy or as treatment after progression). pERC noted that availability of BV as consolidation therapy in the post-ASCT setting may reduce the number of recurrences and hence the need for BV therapy for relapsed disease post-ASCT. pERC noted that the treatment goal of BV consolidation therapy is with curative intent, whereas the treatment goal of BV after failure of ASCT is with palliative intent only.

EVIDENCE IN BRIEF

The CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) deliberated upon:

- A pCODR systematic review
- Other literature in the Clinical Guidance Report that provided clinical context
- An evaluation of the manufacturer's economic model and budget impact analysis (BIA)
- Guidance from the pCODR clinical and economic review panels
- Input from one patient advocacy group: Lymphoma Canada
- Input from registered clinicians
- Input from pCODR's Provincial Advisory Group (PAG).

OVERALL CLINICAL BENEFIT

pCODR Review Scope

The objective of this review is to evaluate the effectiveness and safety of brentuximab vedotin (BV) (Adcetris) for the post-autologous stem cell transplant (ASCT) consolidation treatment of patients with Hodgkin lymphoma (HL) at increased risk of relapse or progression.

Studies Included: One randomized controlled trial

The pCODR systematic review included one phase III, double-blinded, randomized controlled trial: the AETHERA trial. AETHERA evaluated the efficacy and safety of BV consolidation therapy and best supportive care (BSC) compared with placebo plus BSC in patients with HL at increased risk for disease progression/ relapse post-ASCT.

A total of 329 patients were randomized in AETHERA, with 165 assigned to the BV group and 164 to the placebo group. Patients allocated to the active treatment group received BV at a dose of 1.8 mg/kg. BV and placebo were both administered over 30 minutes on day 1 of each 21-day cycle, starting on day 30 up to day 45 post-ASCT, for a maximum of 16 cycles. All patients received BSC that consisted of infection prophylaxis for herpes simplex virus, varicella-zoster virus, and pneumocystis jiroveci post-ASCT, as well as growth factor and blood product support. Dose reductions were permitted according to pre-specified criteria for hematologic and non-hematologic toxicities. Upon radiologic evidence of disease progression/ relapse, as determined by the treating investigator, patients in the placebo group had the option to receive BV as part of a separate clinical study. A total of 73 patients (45%) received BV as subsequent anti-cancer therapy.

Patient Populations: Young patients (median age 32 to 33 years) with refractory Hodgkin lymphoma or relapsed within 12 months of receiving first-line therapy

Trial eligibility criteria required that patients had histologically confirmed classical HL and received high-dose chemotherapy followed by ASCT prior to randomization. Patients had to have at least one of three possible risk factors for disease progression/ relapse post-ASCT, that included: (1) primary refractory HL defined as failure to achieve complete remission (as determined by investigator); (2) relapsed HL with an initial remission duration of < 12 months; or (3) presence of extranodal involvement at the start of pre-ASCT salvage chemotherapy. Only patients with complete or partial remission or stable disease following pre-ASCT salvage chemotherapy were randomized. Adequate organ function and Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 were also eligibility requirements.

The treatment groups were generally well balanced with respect to baseline patient characteristics, with the exception of a higher proportion of female patients (54% versus 41%) and black patients (6% versus 1%) in the BV group. Trial patients were generally young (median age 32 to 33 years) with an ECOG performance status of 0 or 1. The majority of patients in the trial had refractory HL or had relapsed within 12 months of receiving first-line treatment. At the time of salvage therapy, approximately a third of patients presented with extranodal disease. Patients' best response to salvage chemotherapy was as follows: 37% of patients had complete remission, 34% had partial remission, and 28% had stable disease, with 45% of patients receiving at least two salvage therapies.

Key Efficacy Results: Clinically meaningful progression-free survival, immature and confounded overall survival data

The key efficacy outcome deliberated on by pERC was progression-free survival (PFS), which was the primary outcome in the AETHERA trial. PFS was defined as the time from randomization to the first documentation of tumour progression or death. After a median follow-up time of 30 months, PFS, assessed by independent review, was significantly longer in patients treated with BV compared with placebo (hazard ratio [HR] = 0.57; 95% CI, 0.40 to 0.81; p = 0.0013). Median PFS was 42.9 months in the BV group and 24.1 months in the placebo group, which is an improvement of approximately 19 months with BV. pERC agreed with the Clinical Guidance Panel (CGP) that PFS is a clinically meaningful end point for HL patients at increased risk for progression post-ASCT.

The secondary outcomes of the trial included overall survival (OS), safety, and health-related quality of life (QoL).The interim analysis of OS demonstrated no difference between the treatment groups (HR = 1.15; 95% CI, 0.67 to 1.97; p = 0.62). The data are currently deemed immature and are confounded by the subsequent anti-cancer therapies received by patients post-progression. Fifty-one patients (31%) in the brentuximab vedotin group and 85 patients (52%) in the placebo group went on to receive some form of anti-cancer therapy post-progression. Seventy-three patients (45%) in the placebo arm received brentuximab vedotin.

Patient-Reported Outcomes: Modest decrement in quality of life

The EQ-5D (EuroQoL 5-Dimensions) questionnaire was used to measure health-related QoL during treatment and follow-up phases of the trial. The EQ-5D Health State Index assesses health across five dimensions: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. Additional analyses were performed that examined EQ-5D index scores for specific subgroups of patients: those who did/did not experience disease progression post-ASCT (both treatment groups), and those who did/did not experience treatment-emergent peripheral neuropathy (BV group).

Reported adherence in completion of EQ-5D questionnaires was as high (87.5%) and comparable between treatment groups during both the treatment phase and follow-up. In both treatment groups EQ-5D index scores declined over time, with worse scores observed in the BV group compared with placebo following month 6 through to month 18. At most assessment periods the mean differences in index scores between treatment groups were small (< –0.07), except at months 15 and 18, where they met the minimal clinically important difference (MCID) of 0.08. During the treatment phase, mean differences in index scores did not exceed the MCID at any treatment cycle. Patients in both treatment arms who experienced disease progression showed numerically lower mean EQ-5D index scores compared with patients who did not experience disease progression; the MCID was exceeded from months 15 to 24 in the BV group and months 9 to 24 in the placebo arm.

In patients with and without peripheral neuropathy in the BV group, mean differences in EQ-5D index scores did not exceed the MCID at any time point. No differences in mean visual analogue scale (VAS) scores were observed at any time point between the treatment groups. pERC noted that an improvement in QoL in this post-ASCT population in remission or with active lymphoma would be unlikely. The Committee concluded that the AETHERA data did not show a negative effect of BV consolidation therapy on QoL compared with placebo, which pERC considered to be reasonable in the setting of consolidation treatment.

Safety: Manageable toxicity profile

The analysis of adverse events (AEs) was based on a safety population of 167 patients in the BV group and 160 patients in the placebo group. Maintenance therapy with BV after ASCT results in more frequent toxicities compared with placebo. Neutropenia (78%), peripheral sensory neuropathy (56%), thrombocytopenia (41%), and peripheral motor neuropathy (23%) were the most common adverse events. A neutropenia grade > 3 was reported more frequently in the BV arm (BV 39% versus placebo 10%) but did not require dose reductions or treatment discontinuation. Peripheral neuropathy occurred more frequently in the BV group (BV 79% versus placebo 18%), and was the main reason for dose reductions or delays (31%) and treatment discontinuations (23% of patients experiencing dose reductions or delays discontinued treatment). However, pERC noted that of 112 patients in the BV group, 95 (85%) had resolution or improvement of neuropathy symptoms, with a median time to resolution of 23.4 weeks.

During the treatment phase of the trial there was one patient death in the BV group. The patient died within 30 days of receiving the last dose of the study drug from treatment-related acute respiratory distress syndrome (ARDS) associated with pneumonitis.

At the time of primary analysis, 17% (n = 28) of patients in the BV group and 16% (n = 25) of patients in the placebo group had died on study. The majority of deaths were deemed disease-related (i.e., unrelated to study treatment) in both treatment groups (11% in both groups). There were nine (5%) and seven (4%) treatment-related deaths in the BV and placebo groups, respectively. Of note, during the follow-up period, 85 patients (52%) in the placebo group received subsequent therapy after disease progression.

Overall, pERC agreed with CGP that BV can be given safely as consolidation therapy and toxicities can be mitigated with careful dose modification and/or dose delay.

Need and Burden of Illness: Consolidation treatment that prolongs remission with potential to cure

There are approximately 900 new cases of HL in Canada each year and approximately 160 Canadians will die annually from this disease. It is estimated that the annual number of candidates for this use of BV consolidation therapy in Canada is not likely to exceed 100 patients. There is currently no known therapy to improve progression-free or overall survival for patients at increased risk of disease recurrence following ASCT. The CGP agreed with the registered clinicians that observation with best supportive care (BSC) is the only current approach in this setting. Patients who experience relapse after ASCT have very limited treatment alternatives and are generally treated with palliative intent. pERC concluded that there is a significant unmet need for treatments that prolong remission and potentially cure patients with HL at increased risk of relapse or progression/ relapse post-ASCT.

Registered Clinician Input: Need for effective and safe consolidation treatment

The Committee deliberated on input from two clinician groups: one from an individual oncologist and one joint submission from four oncologists.

pERC agreed with the clinicians' input that this indication and reimbursement will affect only a very small number of patients and that observation with BSC is the only current approach in this setting. The key benefit identified by both clinician groups was the clinically meaningful relative improvement in PFS in favour of BV consolidation therapy. An increase in adverse events was identified as a key harm, with the most typical side effects being peripheral neuropathy and hematologic toxicity. However, clinician input suggested that these toxicities can be mitigated with careful dose modification and/or dose delay and that the trial demonstrated that BV consolidation therapy can be given safely in patients after ASCT. pERC agreed with the clinicians providing input that availability of BV as consolidation therapy in the post-ASCT setting may reduce the number of recurrences and hence the need for BV therapy for relapsed disease post-ASCT.

PATIENT-BASED VALUES

Values of Patients With Hodgkin Lymphoma: Disease control and side-effect management

One patient advocacy group, Lymphoma Canada (LC), provided input on BV consolidation therapy for the treatment of patients with HL at increased risk for progression/ relapse post-ASCT.

According to the input received from the patient group, a number of symptoms associated with HL affect QoL, including fatigue or lack of energy, enlarged lymph nodes, drenching night sweats, itching, persistent cough, and mental/emotional problems such as anxiety and difficulties with concentrating. Patients reported on aspects of their life negatively impacted by HL included ability to work, personal image, family obligations, intimate relations, friendships, and ability to attend school. Most respondents indicated that current treatment options (e.g., ABVD [adriamycin, bleomycin, vinblastine, dacarbazine], GDP [gemcitabine, dexamethasone, cisplatin], BEACOPP [bleomycin, etoposide, adriamycin, cyclophosphamide, oncovin, procarbazine, prednisone], MOPP/COPP [mustargen or cyclophosphamide, oncovin, procarbazine, prednisone]), radiation, stem cell transplant, BV and surgery) work well in managing their HL symptoms. LC noted that toxicity associated with their previous treatments were of great concern to many patients, with fatigue, hair loss, nausea/vomiting, "chemo-brain," peripheral neuropathy, loss of menstrual periods, thyroid dysfunction, sterility, and lung damage the most commonly reported side effects. LC also indicated that patients experienced one or more late or long-term treatment-related side effect(s) (lasting longer than two years or appearing later than two years after the end of treatment). Patients providing input expressed that they seek individualized treatment options that will offer disease control and remission, ideally with fewer side effects than current treatments. Patients' expectations about the new drug under review were most importantly "effectiveness" followed by "minimal side effects" or "less side effects than current treatments."

Patient Values on Treatment: Disease control and manageable side effects

According to the input received from the patient group, there are several side effects of BV consolidation therapy, with peripheral neuropathy being one of the more significant concerns. Some of the most common side effects reported with BV included fatigue, peripheral neuropathy, nausea/vomiting, diarrhea, muscle or joint pain, itching, and constipation. The majority of patients responded that, overall, BV had positively affected their health and well-being and that they would take BV again, if their doctor thought it was the best choice. Notably, patients providing input reported, BV had a positive impact on their ability to work and attend school, spend time with family, and participate in activities or travel.

pERC agreed that BV consolidation therapy offers a treatment option with the opportunity to maintain disease control, and has manageable side effects. The Committee concluded that BV consolidation therapy aligned with patient values.

ECONOMIC EVALUATION

Economic Model Submitted: Cost-utility and cost-effectiveness analyses

The pCODR Economic Guidance Panel (EGP) assessed one cost-utility analysis (clinical effects measured by quality-adjusted life-years (QALYs) gained) and one cost-effectiveness analysis (clinical effects measured by life-years gained) of BV consolidation therapy compared with BSC in patients with HL who are at increased risk for progression/ relapse post-ASCT.

Basis of the Economic Model: Clinical and economic inputs

Costs considered in the analyses included drug cost, adverse event cost (not included in BSC arm), remission monitoring cost, post-progression therapy cost, and palliative care costs.

The key clinical outcomes considered in the cost-utility analysis were PFS and OS. pERC noted that in the absence of OS data the model used PFS data as a proxy for overall survival.

Drug Costs: Large incremental costs per patient, given that the comparator is observation only

The unit cost of BV consolidation therapy is $4,840.00 per 50 mg vial. At the recommended dose of 1.8 mg/kg intravenously, every three weeks, BV costs $691.43 per day and $19,360.00 per 28 days. This assumes a total of 126 mg used (using a total of three vials) once per 21-day cycle for an average body weight of 70 kg.

BV consolidation treatment should be continued until a maximum of 16 cycles, disease progression, or unacceptable toxicity, as per the product monograph. The mean and median number of treatment cycles of BV consolation therapy in the AETHERA trial is 12 and 15 cycles, respectively. pERC anticipated that BV consolidation therapy would be associated with wastage given BV is priced per vial, and there are only 50 mg vials available.

Costs of BSC were not explicitly included in the model because both arms would receive it.

Cost-Effectiveness Estimates: Not cost-effective compared with best supportive care, uncertainty due to lack of overall survival data

pERC deliberated upon the cost-effectiveness of BV consolidation therapy in patients with HL at increased risk for progression/ relapse post-ASCT and concluded that BV consolidation therapy is not cost-effective when compared with BSC at the submitted price. pERC noted that the submitted base-case ICER was lower than the EGP's lower and upper bound ICER. This was primarily due to (1) use of independent review-assessed, instead of investigator-assessed, PFS outcomes, (2) a shorter time horizon (15 and 20 years for the upper and lower bound ICERs, respectively, instead of 65 years) and (3) a longer treatment duration (16 cycles instead of 12 cycles as, in the CGP's opinion, patients would not discontinue treatment due to toxicity). pERC noted that according to EGP sensitivity analyses, the factors that most influence the incremental cost of BV consolidation therapy are the drug cost, the treatment duration and the subsequent treatment options. The key effect drivers of the incremental effect are the time horizon and the assessment of PFS (investigator versus independent assessment). Further, the Committee noted the following key limitations of the submitted economic analyses: the lack of OS data from the AETHERA

trial and the resulting uncertainty in the estimates of the incremental cost-effectiveness. pERC noted that in the absence of OS data, the model used PFS data as a proxy for overall survival. Long-term survival was derived from a modelled extrapolation of the Kaplan–Meier PFS curves. pERC agreed with the EGP that this structural limitation increased the uncertainty in the incremental cost-effectiveness. Wastage was included in the submitter's base case as well as in the EGP's reanalysis by assuming that any excess drug in a vial is wasted. Overall, pERC agreed with the EGP's reanalysis and the limitations identified in the submitted economic model. Therefore, pERC accepted the EGP's ICER estimates, which were between a minimum of $105,383/QALY and $139,286/QALY when BV consolidation therapy was compared with BSC. Consequently, pERC concluded that BV consolidation therapy was not cost-effective at the submitted price.

ADOPTION FEASIBILITY

Considerations for Implementation and Budget Impact: Budget impact likely underestimated, drug wastage, and generalizability to patients with other high-risk factors

pERC discussed the feasibility of implementing a reimbursement recommendation for BV consolidation therapy in patients with HL at increased risk for progression/ relapse post-ASCT. pERC discussed that, if BV consolidation therapy were implemented, the market uptake of BV consolidation therapy could be much higher than estimated by the submitter's budget impact analysis (BIA), given that health care professionals are already familiar with its administration in other indications and that adverse events are manageable. pERC acknowledged that, according to the EGP analysis, the submitted BIA was most sensitive to the following changes: (1) assuming a higher market uptake, (2) assuming a longer treatment duration, and (3) increasing the number of HL patients assumed to relapse or to be refractory after frontline therapy. The Committee agreed that jurisdictions will need to consider the uncertainty in these factors upon implementation, and that the BIA is substantially underestimated.

pERC noted the high cost and potential for drug wastage associated with BV consolidation therapy. BV is priced per vial, and there are only 50 mg vials available. pERC noted that BV has 24-hour stability after reconstitution and vial sharing may be unlikely because of the small patient population. pERC agreed that jurisdictions will need to consider mechanisms to minimize wastage upon implementation of a reimbursement recommendation, including advocating for the availability of a smaller vial size.

pERC discussed PAG's request for guidance on a number of clinical scenarios to assist with implementation. pERC discussed that there is currently insufficient evidence to make an informed recommendation on the use of BV consolidation therapy in high-risk patient subgroups, other than those defined in the trial. However, pERC also noted that there is no biological rationale to assume that outcomes of BV consolation therapy would be different in patients with risk factors other than those defined in the AETHERA trial. pERC suggested that jurisdictions may want to develop a national consensus on a possible broader definition of increased risk. Additional high-risk features may include: B symptoms, less than complete response to salvage therapy as assessed by computed tomography (CT) or positron emission tomography (PET) scan, relapse in a prior radiation field, or the requirement of more than one line of salvage therapy pre-ASCT.

Further, pERC noted that there is currently insufficient evidence to make an informed recommendation on re-treatment with BV. pERC noted that re-treatment of patients with BV who (1) have received and responded to BV pre-ASCT, or (2) who have relapsed after receiving BV consolidation therapy post-ASCT, is out of scope of this review. pERC agreed with the CGP's speculation that, rather than re-treatment with BV, clinicians might move to other options, such as PD-1 inhibitors.

DRUG AND CONDITION INFORMATION

Drug Information	• CD30-directed antibody-drug conjugate • Single-use vial containing 50 mg of ADCETRIS as lyophilized powder for reconstitution • 1.8 mg/kg administered only as an intravenous infusion over 30 minutes every 3 weeks. ADCETRIS treatment should be initiated within 4-6 weeks post-autologous stem cell transplant (ASCT) or upon recovery from ASCT and continued until a maximum of 16 cycles, disease progression, or unacceptable toxicity
Cancer Treated	• Hodgkin lymphoma (HL)
Burden of Illness	• There are approximately 900 new cases of HL in Canada each year and approximately 160 Canadians will die annually from this disease. It is estimated that the annual number of candidates for this use of brentuximab vedotin (BV) in Canada is not likely to exceed 100 patients
Current Standard Treatment	• Observation only with best supportive care
Limitations of Current Therapy	• No consolidation therapy

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee

Recommendations are made by the CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) following the pERC Deliberative Framework. pERC members and their roles are as follows:

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice Chair)
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Matthew Cheung, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Craig Earle, Oncologist
Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Cameron Lane, Patient Member Alternate
Valerie McDonald, Patient Member
Carole McMahon, Patient Member
Dr. Marianne Taylor, Oncologist

All members participated in deliberations and voting on the Initial Recommendation, except:

- Dr. Kelvin Chan, Dr. Winson Cheung and Dr. Craig Earle who were not present for the meeting
- Cameron Lane did not vote due to his role as a patient member alternate

Avoidance of conflicts of interest

All members of the pCODR Expert Review Committee must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of brentuximab vedotin (Adcetris) for Hodgkin lymphoma (HL) (post-ASCT consolidation), through their declarations, no members had a real, potential or perceived conflict and based on application of the

pCODR Conflict of Interest Guidelines, none of these members was excluded from voting.

Information sources used

pERC is provided with a pCODR Clinical Guidance Report and a pCODR Economic Guidance Report, which include a summary of patient advocacy group and Provincial Advisory Group input, as well as original patient advocacy group input submissions, to inform its deliberations. pCODR guidance reports are developed following the pCODR review process and are posted on the pCODR website. Please refer to the pCODR guidance reports for more detail on their content.

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*.

Use of this Recommendation

This Recommendation from pERC is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policy-makers make well-informed decisions and improve the quality of health care services. While patients and others may use this Recommendation, it is for informational and educational purposes only, and should not be used as a substitute for the application of clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

Disclaimer

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APPENDIX 1: pERC RESPONSES TO PAG IMPLEMENTATION QUESTIONS

PAG Implementation Questions	pERC Recommendation
• PAG is seeking clarity on the benefits of treatment with BV in earlier stage of disease (i.e., as consolidation treatment post-autologous stem cell transplant (ASCT) compared with later stage (i.e. upon relapse or progression post-ASCT).	• pERC noted that the overall survival analysis in the AETHERA trial was immature and confounded by the high cross-over rate of patients in the placebo group to brentuximab vedotin (BV). Importantly, this precluded a conclusion on the optimal timing of brentuximab (that is, as consolidation therapy versus treatment after progression). pERC noted that availability of BV as consolidation therapy in the post-ASCT setting may reduce the number of recurrences and hence the need for BV therapy for relapsed disease post-ASCT.
• The Provincial Advisory Group (PAG) is seeking clarity on defining the patient population considered at an increased risk of relapse or progression/ relapse post-ASCT, who would be eligible for treatment with BV consolidation therapy. In particular, PAG is seeking guidance for patients who are at high risk of disease progression/ relapse post-ASCT with features not captured in the AETHERA trial definition of high risk. These may include: 1. Less than a complete response to salvage therapy, as assessed by computed tomography (CT) or positron emission tomography scan 2. Relapse in prior radiation field 3. B symptoms or stage IV at relapse	• There is currently insufficient evidence to make an informed recommendation on the use of BV consolidation therapy in high-risk patient subgroups, other than those defined in the trial. However, pERC noted that there is no biological rationale to assume that outcomes of BV consolation therapy would be different in patients with other risk factors than those defined in the AETHERA trial. pERC suggested that jurisdictions may want to develop a national consensus on a possible broader definition of increased risk.
• PAG is seeking guidance on whether patients who received and responded to BV prior to ASCT would be eligible to receive and likely respond to BV as consolidation treatment post-ASCT. • PAG is seeking guidance on whether patients who receive BV consolidation therapy and subsequently relapse would be eligible to receive BV treatment and whether they would be likely to respond. • PAG is seeking guidance on treatment options for patients who relapse after BV consolidation therapy.	• There is currently insufficient evidence to make an informed recommendation on re-treatment with BV. pERC noted that re-treatment of patients with BV who (1) have received and responded to BV pre-ASCT, or (2) who have relapsed after receiving BV consolidation therapy post-ASCT, is out of scope of this review. pERC agreed with the CGP that, rather than re-treatment with BV, clinicians might move to other options, such as PD-1 inhibitors, if available.
• PAG noted that drug wastage is an issue as vial sharing may be unlikely.	• pERC agreed and noted the high cost and potential for drug wastage associated with BV consolidation therapy. BV is priced per vial, and there are only 50 mg vials available. pERC noted that BV has 24-hour stability after reconstitution and vial sharing may be unlikely, because of the small patient population. pERC agreed that jurisdictions will need to consider mechanisms to minimize wastage upon implementation of a reimbursement recommendation, including advocating for the availability of a smaller vial size.