pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL 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.

pERC Final Recommendation
This pERC Final Recommendation is based on a reconsideration of the Initial Recommendation and feedback from eligible stakeholders. This pERC Final Recommendation supersedes the pERC Initial Recommendation.

Drug: Brentuximab Vedotin (Adcetris) **Submitted Reimbursement Request:** For the treatment of previously untreated patients with stage IV Hodgkin lymphoma in combination with doxorubicin, vinblastine, and dacarbazine.	
Submitted By: Seattle Genetics, Inc.	**Manufactured by:** Seattle Genetics, Inc.
NOC Date: May 2, 2019	**Submission Date:** April 2, 2020
Initial Recommendation: October 1, 2020	**Final Recommendation:** December 3, 2020

Approximate per Patient Drug Costs, per Month (28 Days)	Brentuximab vedotin costs $4,840 per 50 mg vial. At the recommended dose of 1.2 mg/kg administered intravenously on days 1 and 15 of each 28-day cycle (up to a maximum of six cycles), brentuximab vedotin costs $19,360 per 28-day cycle. Brentuximab vedotin in combination with doxorubicin, vinblastine, and dacarbazine costs $21,579 per 28-day cycle.

pERC RECOMMENDATION

☐ **Reimburse**

☒ **Reimburse with clinical criteria and/or conditions***

☐ **Do not reimburse**

*If the condition(s) cannot be met, pERC does not recommend reimbursement of the drug for the submitted reimbursement request.

pERC conditionally recommends reimbursement of brentuximab vedotin (BV) in combination with doxorubicin, vinblastine, and dacarbazine (AVD) for the treatment of previously untreated patients with stage IV Hodgkin lymphoma (HL), if the following condition is met:

- cost-effectiveness being improved to an acceptable level

Treatment should be continued until disease progression, unacceptable toxicity, or until a maximum of six cycles, whichever comes first.

pERC made this recommendation because it was satisfied that BV in combination with AVD may have a net clinical benefit compared with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) for patients with previously untreated stage IV HL based on clinically meaningful improvements in modified progression-free survival (mPFS) in the intention-to-treat population and the prespecified subgroup of stage IV patients. However, pERC recognized the uncertainty around the magnitude of the mPFS benefit with BV in combination with AVD in the subgroup of stage IV patients given that the ECHELON-1 trial was not designed nor powered to detect specific treatment effects or test specific hypotheses within individual subgroups. pERC acknowledged that BV in combination with AVD had considerable but manageable toxicities with no significant detriment to quality of life (QoL). pERC noted a need for treatment options that lead to long-term remission and potential cure. Furthermore, pERC could not conclude on the relative efficacy and safety of BV in combination with AVD compared with PET-scan guided approaches

	given the lack of direct comparative data. pERC noted that PET-guided treatment approaches are commonly used in Canada. In addition, pERC noted that there is currently insufficient evidence to inform the use of PET-scan guided approaches for patients who have started on BV in combination with AVD therapy. pERC also concluded that BV in combination with AVD aligns with the following patient values: offers disease control and remission as well as an individualized treatment choice. The Committee concluded that, based on the sponsor's economic analysis and at the submitted price, BV in combination with AVD is not considered cost-effective compared with ABVD. pERC noted that the results of the analysis were driven by the high cost of BV, and that uncertainty remained due to limitations with the sponsor's submitted model. pERC indicated that a price reduction of BV would be required for BV in combination with AVD to be cost-effective. pERC also concluded that the budget impact associated with the uptake of BV in combination with AVD at the submitted price for BV would vary depending on the market uptake compared with PET-scan guided approaches.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Pricing Arrangements to Improve Cost-Effectiveness and Decrease Budget Impact** Given that pERC was satisfied that there may be a net clinical benefit of BV in combination with AVD, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of BV in combination with AVD. pERC noted that a substantial reduction in the price of BV would be required in order to improve the cost-effectiveness and to decrease the predicted budget impact. **Possibility of Submission to Support Reimbursement of BV in Combination With AVD for Stage III HL** pERC noted that current Canadian practice is to offer the same treatments to patients with stage III and IV disease, however, pERC highlighted that the Health Canada (HC) approved indication was limited to patients with stage IV. Updated efficacy analyses after 3- and 4-year follow-up reported exploratory PFS data, which were not included in the HC assessments. pERC noted that updated clinical and economic data comparing BV in combination with AVD with currently available treatments in Canada for patients with previously untreated stage III HL, could form the basis of a new submission to CADTH pending a submission for regulatory approval. **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

pERC's *Deliberative Framework* for drug reimbursement recommendations focuses on four main criteria:

CLINICAL BENEFIT	**PATIENT-BASED VALUES**
ECONOMIC EVALUATION	**ADOPTION FEASIBILITY**

Hodgkin lymphoma (HL) is an uncommon cancer. In 2020, it is estimated that 1,000 new cases of HL will be diagnosed and 100 deaths will occur in Canada. Classical Hodgkin lymphoma (cHL) accounts for 95% of HL cases and is characterized by the presence of CD30+ Reed-Sternberg cells. Of all newly diagnosed patients, approximately 23.3% of patients were diagnosed with stage III and 22.7% with stage IV disease. The average five-year relative overall survival (OS) is 80% and 65% in patients with stage III and IV disease, respectively. Patients with stage III and IV disease are managed similarly according to advanced stage disease treatment protocols. Current standard frontline treatment for advanced stage disease is doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD). An alternative regimen for young and healthy patients is BEACOPP (bleomycin/etoposide/doxorubicin/ cyclophosphamide/vincristine/procarbazine/prednisone), which is not commonly used in Canada due to its toxicity profile. More recently, fluorodeoxyglucose-positron emission tomography (FDG-PET) scan adapted therapy has emerged, which uses interim PET-scan results to direct treatment decisions; individuals classified as having high-risk disease based on interim PET-scan results may undergo treatment intensification; whereas, patients with lower-risk disease may be eligible for treatment de-escalation (e.g., initially ABVD for two cycles and then escalation to BEACOPP or de-escalation to AVD). Uptake of this adaptive strategy varies by region but is being adopted by an increasing number of treatment centres across Canada. Overall, HL is generally regarded as a curable disease; however, up to 30% of patients with advanced disease experience disease progression. pERC agreed with the pCODR Clinical Guidance Panel (CGP) and the registered clinicians providing input that there is still an unmet need in advanced cHL for more effective therapies with tolerable toxicity and the potential for long-term remission and cure.

pERC deliberated on the results of one randomized, multi-national, open-label, phase III trial (ECHELON-1) that evaluated the efficacy and safety of BV in combination with AVD compared with the combination regimen of ABVD in patients with previously untreated advanced cHL. pERC noted that the reimbursement request was specifically for the subgroup of patients with stage IV disease; whereas, the trial population also included patients with stage III disease. pERC considered that mPFS, the primary outcome of the trial, was statistically significant and clinically meaningful in favour of BV in combination with AVD. While patients with stage IV disease represented the largest subgroup within the trial, pERC acknowledged that there was uncertainty around the magnitude of the mPFS benefit for this patient subgroup. pERC noted that subgroup analyses were considered exploratory because the ECHELON-1 trial was not designed to test specific hypotheses for subgroups. pERC noted that CD30-expression is the target for the mechanism of action of BV and that there is no apparent biological rationale to assume that outcomes of BV in combination with AVD therapy would be different between stage III and IV disease. Upon reconsideration of the Initial Recommendation, the Committee discussed feedback provided by PAG noting that stage III and IV patients with HL are treated the same in clinical practice and eligibility for BV in combination with AVD for stage III is a key implementation issue. In response to the feedback, pERC agreed with PAG and the CGP that Canadian clinicians universally offer the same treatments to patients with stage III and IV disease. pERC reiterated that there is no biological or clinical rationale to assume that treatment effect of BV in combination with AVD therapy would be different between stage III and IV disease. Furthermore, pERC reiterated that the HC-approved indication and subsequently the reimbursement request are for only stage IV disease; therefore, pERC was unable to recommend BV in combination with AVD for patients with stage III disease. pERC highlighted that the HC approved indication was limited to patients with stage IV disease, although the sponsor's request to HC included the full trial population. HC noted uncertainties regarding efficacy (including inconsistency in observed mPFS benefit between stage III and IV subgroups, immature OS data, and use of a surrogate end point); and increased SAEs in stage III patients compared to stage IV, which deemed the benefit-risk profile to be positive only for patients with stage IV disease. HC's final decision was based on the totality of evidence showing that the benefit of BV in combination with AVD was most substantial in patients with stage IV disease.

OS data were immature at the time of the primary efficacy analysis and pERC noted that with additional follow-up, the OS data will likely still be confounded by the post-trial treatments given after disease progression. In the absence of mature OS data, pERC expressed some concern about mPFS being a novel end point for HL and that it has not been established as a surrogate end point for OS. However, pERC agreed with the CGP that mPFS is a clinically meaningful end point in advanced HL given it includes progression events and that it reflects the curative intent of frontline therapy by identifying patients who receive subsequent treatment due to noncomplete response. pERC further discussed that the likelihood of cure diminishes with each subsequent line of therapy and only a proportion of patients may be candidates for autologous stem cell transplant (ASCT); treatment options for patients who are ineligible to receive ASCT are treated with palliative intent only. pERC also considered a post-hoc analysis of the exploratory outcome progression-free survival (PFS), at three- and four-years follow-up, that suggested that the benefit was maintained in the overall trial population and also suggested favourable effects in subgroups of patients with both stage III and IV disease. Overall, pERC agreed with the CGP and the registered clinicians providing input that the mPFS benefit observed in patients with stage IV disease is of clinical importance in the setting of advanced stage HL.

pERC discussed the toxicity profile of BV in combination with AVD and noted that the incidence of all-grade treatment-emergent adverse events (TEAEs) was broadly similar between study groups. However, a higher incidence of severe TEAEs (Grade ≥ 3), serious TEAEs, and drug-related AEs were reported for the patients treated with BV in combination with AVD compared with ABVD, mainly related to neutropenia. Higher than or equal to Grade 3 TEAEs occurred more frequently in the BV in combination with AVD group and included: neutropenia, febrile neutropenia, anemia, peripheral sensory neuropathy, peripheral neuropathy, and infections. pERC noted that the implementation of granulocyte colony-stimulating factor (G-CSF) prophylaxis in patients receiving BV in combination with AVD resulted in a reduction of neutropenia and infection. Most patients who had developed peripheral neuropathy while receiving BV in combination with AVD had experienced either resolution or improvement at the time of last patient follow-up. Pulmonary toxicity was reported in a small number of patients in the trial but was more frequent in the ABVD group. Overall, pERC concluded that BV in combination with AVD had considerable but manageable toxicities.

pERC discussed the available patient-reported outcomes data from the ECHELON-1 trial and noted that overall quality of life (QoL) was similar between study groups and did not show a significant negative effect of BV in combination with AVD on QoL compared with AVD. A slight trend of unfavourable scores in the BV in combination with AVD group was observed during the treatment period, but scores showed no clinically meaningful differences between the two groups and had returned to at least baseline value during the post-treatment follow-up period. pERC also considered that the neurotoxicity subscale scores showed greater symptoms of neuropathy in the BV in combination with AVD group during treatment, which was consistent with the higher proportion of patients experiencing peripheral neuropathy in that group. Overall, pERC agreed that BV in combination with AVD had no significant detriment to QoL.

Furthermore, pERC discussed other currently relevant treatment options for advanced HL. pERC noted that since the initiation of the ECHELON-1 trial, PET-scan guided approaches have emerged and are increasingly adopted in treatment centres across Canada. pERC could not draw conclusions regarding the relative efficacy and safety of BV in combination with AVD compared with PET-scan guided approaches given the lack of comparative data. pERC discussed that there may be interprovincial and inter-clinician variability in choosing the optimal treatment. pERC agreed with some registered clinicians providing input to this submission that BV in combination with AVD may be used as a complementary treatment in case of tolerability or accessibility concerns with treatments that are currently available. pERC discussed that in rural areas PET scans are not routinely available and patients would have to travel several hours to reach a treatment centre that offers this procedure. In addition, pERC agreed with the CGP that there is currently insufficient evidence to inform the use of PET-scan guided approaches for patients who have started on BV in combination with AVD treatment.

In summary, pERC concluded that BV in combination with AVD may have a net clinical benefit compared with ABVD for patients with previously untreated stage IV HL based on clinically meaningful improvements in mPFS. pERC also acknowledged that BV in combination with AVD had considerable but manageable toxicities with no significant detriment to quality of life. pERC noted a need for treatment options that lead to long-term remission and potential cure. However, pERC recognized the uncertainty around the magnitude of the mPFS benefit with BV in combination with AVD given that the ECHELON-1 trial was not designed to detect treatment effects within subgroups. Furthermore, pERC noted that PET-scan guided

treatment approaches are currently commonly used in Canada. pERC could not conclude on the relative efficacy and safety of BV in combination with AVD compared with PET-scan guided approaches given the lack of comparative data. pERC noted that there is currently insufficient evidence to guide the use of PET-scan guided approaches to adapt treatment at earlier cycles for patients who have started on BV in combination with AVD therapy.

pERC deliberated the patient advocacy group input from Lymphoma Canada (LC). pERC noted that, according to patients, key symptoms of concern with HL included: fatigue, enlarged lymph nodes, drenching night sweats, itching, persistent cough, unexplained weight loss, loss of appetite, trouble breathing, fever/chills, and chest pain. Anxiety/worry was reported as the most common symptom that significantly impacted patients' QoL. A few patients who had direct experience using BV in combination with AVD indicated the following side effects: peripheral neuropathy, neutropenia, fatigue, and nausea/vomiting. According to LC, most patients with experience with BV in combination with AVD noted that they would be willing to tolerate significant side effects in exchange for the chance at longer remission or cure. All patients with direct experience concluded that BV in combination with AVD had overall improved their health and wellbeing. pERC concluded that the use of BV in combination with AVD aligned with the following patient values: offers disease control and remission as well as an individualized treatment choice. Given the toxicity profile of the BV combination, pERC noted that it did not align with the patient value of minimal or reduced side effects.

pERC deliberated on the cost-effectiveness of BV in combination with AVD compared to ABVD. pERC discussed the limitations of the submitted model described by the Economic Guidance Panel (EGP) and noted that uncertainty remained due to key limitations such as the rate of use and efficacy of BV consolidation therapy following ASCT and issues relating to the cost of subsequent lines of chemotherapy. pERC considered the reanalyses conducted by the EGP, which incorporated a number of key changes to the model to address limitations. These changes included the use of mPFS data as assessed by an independent review facility instead of assessed by an investigator, adjustments to the costs of chemotherapy following frontline failure, limiting the impact of pulmonary toxicity on mortality to five years, and assuming a lower proportion of patients on ABVD receive G-CSF prophylaxis. pERC concluded that BV in combination with AVD was not cost-effective at the submitted price for BV at conventional willingness-to-pay thresholds, and that a substantial price reduction of BV would be required for BV in combination with AVD to be considered cost-effective. pERC also noted that the generalizability of these results to Canadian clinical practice was highly uncertain given that the sponsor's submitted analysis did not consider PET-adaptive regimens. Such regimens are the standard of care in many practice settings in Canada where PET scans are accessible.

pERC also discussed the budget impact analysis and noted that the factor most influencing the estimated budget impact was the estimated market uptake of BV. pERC noted that the EGP considered the market uptake calculated by the sponsor to be underestimated, and that the use of an updated estimate by the EGP yielded a higher overall budget impact when compared to the sponsor's estimate.
The generalizability of the assumed market uptake of BV and the model results to the Canadian context was of concern given that PET-adaptive regimens were not considered. pERC anticipates a more limited market uptake of BV than that of the CADTH reanalysis when considering settings where PET-adaptive regimens are available, as PET-adaptive regimens which incorporate ABVD are the standard of care in many clinical practice settings in Canada and are less likely to be displaced by BV in combination with AVD. pERC estimated that within the PET-adaptive context, the market uptake and resulting budget impact from the introduction of BV in combination with AVD was likely to be somewhere between the sponsor's assessment and the EGP's reanalysis, though this remains uncertain.

Upon reconsideration of the Initial Recommendation, pERC noted that although the ECHELON-1 study included patients with previously untreated advanced cHL (stage III/IV), the sponsor's submitted model and budget impact analysis did not include patients with stage III disease making a proper evaluation challenging.

The Committee deliberated on the input from PAG, regarding factors related to currently funded treatments, the eligible population, implementation factors, and sequencing and priority of treatment. Refer to the summary table in Appendix 1 for more details.

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 sponsor's economic model and budget impact analysis
- guidance from the pCODR clinical and economic review panels
- input from one patient advocacy group (Lymphoma Canada)
- input from registered clinicians: one joint clinician on behalf of five clinicians from Lymphoma Canada, and one individual clinician input from Cancer Care Ontario (CCO)
- input from pCODR's Provincial Advisory Group (PAG).

Feedback on the pERC Initial Recommendation was also provided by:

- one clinician from Cancer Care Ontario (CCO)
- the PAG
- the sponsor Seattle Genetics, Inc.

The pERC Initial Recommendation was to recommend reimbursement of BV in combination with AVD for the treatment of previously untreated patients with stage IV HL, if the following condition is met:

- cost-effectiveness being improved to an acceptable level.

Feedback on the pERC Initial Recommendation indicated that the registered clinician and the sponsor agreed with the Initial Recommendation. PAG did not agree with the Initial Recommendation and did not support early conversion of the Initial Recommendation to a Final Recommendation. No feedback was received from the patient advocacy group.

OVERALL CLINICAL BENEFIT

pCODR Review Scope

The purpose of the pCODR review was to evaluate the safety and efficacy of BV, in combination with doxorubicin, vinblastine, and dacarbazine (AVD), compared with standard of care in Canada for previously untreated patients with stage IV Hodgkin lymphoma (HL).

Studies included: One ongoing, international, open-label, randomized phase III trial (ECHELON-1)

The CADTH systematic review included one randomized controlled trial (RCT) (ECHELON-1) that assessed the efficacy and safety of BV in combination with AVD compared with ABVD in patients with advanced HL (stages III and IV).

A total of 1,334 patients were randomized on a 1:1 ratio to receive either BV in combination with AVD (1.2 mg/kg of BV, 25 mg/m^2 of doxorubicin, 6 mg/m^2 of vinblastine, and 375 mg/m^2 of dacarbazine) (n = 664) or ABVD (25 mg/m^2 of doxorubicin, 10 units/m^2 of bleomycin, 6 mg/m^2 of vinblastine, and 375 mg/m^2 of dacarbazine) (n = 670). Treatments in both study groups were administered on day 1 and 15 of each 28-day cycle for a maximum of six cycles. In both BV in combination with AVD and ABVD treatment groups, patients received a median of six treatment cycles (range 1 to 6), administered over a median duration of approximately 24 weeks (range 2.0 to 48.9 weeks). The median relative dose intensity of each drug in both groups ranged from 99% to 100%.

Patients were included in the trial if they met the following key criteria: adults with treatment-naive stage III or IV histologically confirmed classic Hodgkin lymphoma (cHL) and an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to 2. Patients with nodular lymphocyte-predominant Hodgkin lymphoma as well as those with sensory or motor peripheral neuropathy were excluded.

Patient populations: Median age 36, baseline characteristics well balanced

Baseline demographics and clinical characteristics were generally well balanced between the two treatment groups. Overall, the median age of enrolled patients was 36 years (range 18 to 83 years); most (66%, 874 of 1,334) were younger than 45 years and 14% (186 of 1,334) were 60 years or older. Of the total number of patients enrolled, 58% (n = 776) were male and 84% (n = 1,114) were White. Notably, a majority of patients had stage IV disease (64%, n = 846), International Prognostic Score of 2 or 3 (53%, n = 705), ECOG PS of 0 (57%, n = 754), extranodal involvement at diagnosis (62%, n = 827), and B symptoms (59%, n = 781) at baseline.

Key efficacy results: Clinically meaningful improvement in mPFS in favour of BV in combination with AVD

The primary end point was modified progression-free survival (mPFS) per independent review facility (IRF), which was defined as time from the date of randomization to the date that the first of the following occurred: documentation of progressive disease; death due to any cause; or modified progression. Modified progression was defined as achievement of noncomplete response (Deauville Score 3, 4, or 5) confirmed by an independent committee plus receipt of subsequent anticancer treatment. As of the primary data cut-off date (April 20, 2017) for final mPFS analysis and interim OS analysis, median mPFS had not been reached in either treatment group. Overall, 263 mPFS events had been observed: 117 (17.6%) in the BV in combination with AVD group and 146 (21.8%) in the ABVD group, mostly due to disease progression. A small proportion of patients (n = 9, 1% of BV in combination with AVD; n = 22, 3% of ABVD group) experienced modified progression, most of whom received salvage chemotherapy as subsequent treatment; two patients treated with BV in combination with AVD and seven patients with ABVD received radiotherapy.

The two-year mPFS rate was higher in patients treated with BV in combination with AVD compared to ABVD (82.1% versus 77.2% respectively), with a hazard ratio (HR) of 0.77 (95% CI, 0.60 to 0.98; P = 0.04) for progression, death, or modified progression. This corresponds with a 23% risk reduction in mPFS favouring BV in combination with AVD treatment. Most results of the pre-specified exploratory mPFS subgroup analyses were consistent with the results of mPFS in the intention-to-treat (ITT) population with some subgroups of patients appearing to derive more benefit with BV in combination with AVD compared with ABVD than others, including patients with stage IV disease with an unstratified HR of 0.71 (95% CI, 0.53 to 0.96). The subgroup analyses are considered exploratory because the ECHELON-1 trial was not designed to test specific hypotheses for treatment effects in individual subgroups of patients.

An updated post-hoc exploratory analysis of investigator-assessed PFS after three and four years of follow-up showed maintained benefit in the ITT population as well as for both stage III and IV disease.

The interim analysis of OS demonstrated no statistically significant difference between treatment groups (HR 0.73; 95% CI, 0.45 to 1.18). The data are currently immature (i.e., median OS not reached in both study groups), with the final analysis of OS data planned for after 112 deaths have occurred. At the time of data cut-off, 67 deaths were reported, with 28 deaths in BV in combination with AVD and 39 deaths in ABVD groups, with estimated two-year interim OS rates of 96.6% and 94.2% for patients treated with BV in combination with AVD and ABVD, respectively. Final OS analysis was still not performed at the time of the four-year follow-up.

Patient-reported outcomes: Overall no significant difference between treatment groups; greater symptoms of neuropathy in BV combination group

In the ECHELON-1 trial health-related quality of life (HRQoL) was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30), Functional Assessment of Chronic Illness Therapy — Dyspnea (FACIT-Dyspnea 10), Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx), and EuroQoL 5-Dimension (EQ-5D-3L) instruments.

For the (EORTC QLQ-C30) subscale scores of global health status/QoL showing change from baseline to end of treatment, there was generally a decrease in scores in the BV in combination with AVD group and increase in scores in the ABVD group; however, the differences between the two groups were below the specified minimally important difference, thus deemed not clinically meaningful. Similarly, mean summary scores over time across treatment cycles were lower in the BV in combination with AVD group; however, during post-treatment follow-up, scores had returned to baseline levels or better. [redacted]

[redacted]. A clinically meaningful difference was seen in the FACT/GOG-Ntx neurotoxicity subscale scores during cycle 4 to 6, indicating greater symptoms of neuropathy (and worse quality of life) in patients treated with BV in combination with AVD. There was no difference seen in the EQ-5D-3L mean scores between the two treatment groups.

Safety: considerable but manageable toxicities

The incidence of all-grade treatment-emergent adverse events (TEAEs) was broadly similar between study groups. TEAEs were reported in 653 (99%) and 646 (98%) of patients in the BV in combination with AVD and ABVD groups, respectively. Compared with the ABVD group, the BV in combination with AVD group had a higher incidence of severe TEAEs (Grade ≥ 3) (83% versus 66%), serious TEAEs (43% versus 27%), and drug-related AEs (97% versus 94%), which was mainly due to neutropenia. The most reported Grade ≥ 3 TEAEs occurring more frequently in the BV in combination with AVD group included neutropenia (54% versus 39%), febrile neutropenia (19% versus 8%), anemia (8% versus 4%), peripheral sensory neuropathy (5% versus < 1%), and peripheral neuropathy (4% versus < 1%).
A higher rate of infections was reported in the BV in combination with AVD group, before implementing G-CSF prophylaxis. Initially, infections (of any grade) were reported in 55% of patients (n = 361) in the BV in combination with AVD group and 50% (n = 331) in the ABVD group; infections of greater than or equal to Grade 3 were reported in 18% of patients (n = 116) treated with BV in combination with AVD and in 10% (n = 66) of patients treated with ABVD. After implementation of G-CSF primary prophylaxis, the incidence of febrile neutropenia and infections overall decreased, although it remained higher in the BV in combination with AVD group compared to ABVD.

Pulmonary-related toxicity (i.e., related to interstitial lung disease) of any grade occurred in 2% of patients (12 of 662) receiving BV in combination with AVD compared to 7% of patients (44 of 659) treated with ABVD. Specifically, lung infiltration and pneumonitis were the most frequently reported pulmonary-related toxicity in patients treated with BV in combination with AVD; whereas pneumonitis, pulmonary toxicity, and interstitial lung disease were reported most frequently in patients treated with ABVD. Grade 3 or higher pulmonary toxicity was reported in fewer than 1% (n = 5) and 3% (n = 21) of patients in the BV in combination with AVD and ABVD groups, respectively. Similarly, interstitial lung disease reported as a SAE was seen in fewer than 1% of BV in combination with AVD and 3% of ABVD patients. Incidence of pulmonary-related toxicity was also higher in older patients who received ABVD, but no age correlation was seen in the BV in combination with AVD group.

Patients who had stage IV disease at baseline experienced similar proportion of TEAEs and drug-related AEs between the two treatment groups. Similar to the overall population, there was higher incidence of greater than or equal to Grade 3 TEAEs and serious TEAEs noted in the BV in combination with AVD group. Of the safety population with stage IV disease who experienced a greater than or equal to Grade 3 TEAE (reported in at least 10% in each group), neutropenia was also most common (56%, 239 of 424 patients in BV in combination with AVD; 41%, 169 of 413 in ABVD), followed by febrile neutropenia (19%, 80 of 424 patients in BV in combination with AVD; 8%, 35 of 413 in ABVD). Febrile neutropenia (17% BV in combination with AVD versus 7% ABVD) and pyrexia (6% BV in combination with AVD versus 5% ABVD) were the most frequent serious TEAEs (reported in at least five patients in either group).

Rate of hospitalization (37% in BV in combination with AVD, 28% in ABVD), which were mainly due to adverse events of treatment, were higher than normally expected in the Canadian setting according to the CGP. This may reflect a difference in method of monitoring, mitigation, or treatment of adverse effects for patients in the trial compared to the Canadian patient population. Rate of infusion-related reactions in the ABVD arm (15%, versus 9% in the BV in combination with AVD group) were also greater than normally expected in the Canadian patient population.

During the on-study treatment phase (within 30 days after last dose of frontline therapy), eight of the nine deaths in the BV in combination with AVD group were deemed to be due to a drug-related AE. Of the treatment-related deaths, seven were associated with neutropenia and its complications such as neutropenic sepsis and septic shock; the deaths occurred in patients who did not receive G-CSF primary prophylaxis. In the ABVD group, seven out of the 13 on-study deaths were deemed to be drug-related, with the majority being due to pulmonary-related toxicity.

Limitations: Subgroup analyses by disease stage exploratory

The CADTH Methods Team noted several key limitations including the following:

- The population of the ECHELON-1 trial was broader than the reimbursement request for this CADTH submission. Patients with stage III and IV were eligible for inclusion into the trial. However, this reimbursement request was limited to patients with stage IV disease only. While baseline cancer stage (stage III, IV) was a pre-specified subgroup for the primary outcome, mPFS, the ECHELON-1 trial was not designed or powered to test specific hypotheses in individual subgroups of patients. The mPFS subgroup results are therefore exploratory and considered to be hypothesis generating only.
- The updated efficacy analysis performed after three- and four-years patient follow-up reported traditional PFS, which was an exploratory analysis. These updated results should be interpreted with caution as the trial was not originally designed to measure PFS, and this end point was measured by investigators, which is subject to bias.
- The study was unblinded with an open-label protocol; the investigators, patients, and sponsor were aware of the patients' treatment allocation. However, the sponsor's study team, investigators, and patients were blinded to aggregate efficacy data and the IRF that measured the primary outcome was blinded to treatment.
- The primary end point selected by investigators (mPFS) is novel and includes modified progression in order to capture all events that reflect a failure of frontline chemotherapy; however, this makes cross-trial comparisons (to trials reporting on traditional PFS) difficult. Also, the strength of the association between surrogate outcomes, such as mPFS or PFS, and overall survival is unknown.
- The definition of mPFS is different from the established PFS definition by including modified progression, defined as a noncomplete PET response (Deauville score 3, 4, or 5 on PET scan confirmed by an independent committee) after completion of frontline therapy, with subsequent receipt of anticancer treatment. Of those who experienced a modified progression event, seven out of nine patients in the BV in combination with AVD group and 15 out of 22 patients in the ABVD group received subsequent salvage chemotherapy, and the remainder (two patients in BV in combination with AVD, seven patients in ABVD) received radiation therapy. There is potential bias from investigator subjectivity within the decision to use subsequent anticancer therapy (chemotherapy or radiotherapy). However, effort was made to limit the risk of bias by having PET-scan results assessed and the decision to offer subsequent chemotherapy made independently and centrally. Overall, given the small number of patients who received first subsequent anticancer therapy as part of salvage treatment for failing to achieve a complete response at the completion of frontline therapy, the impact of potential bias from investigator subjectivity within the decision to use subsequent anticancer therapy on overall trial results is likely limited.

Need and burden of illness: Average five-year survival rate of 65% with stage IV disease; currently common treatment options include ABVD and PET-scan guided approaches

Hodgkin lymphoma (HL) is an uncommon cancer. In 2020, it is estimated that 1,000 new cases of HL will be diagnosed and 100 deaths will occur in Canada. Classical Hodgkin lymphoma (cHL) accounts for 95% of HL cases and is characterized by the presence of CD30+ Reed-Sternberg cells. Of all newly diagnosed patients, approximately 23% of patients were diagnosed with stage III and stage IV disease. The average five-year relative overall survival (OS) is 80% and 65% in patients with stage III and IV disease, respectively. Patients with stage III and IV disease are managed similarly according to advanced stage disease treatment protocols. Current standard frontline treatment for advanced stage disease is doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD). An alternative regimen for young and healthy patients is BEACOPP (bleomycin/etoposide/doxorubicin/cyclophosphamide/vincristine/procarbazine/prednisone), which is not commonly used in Canada due to its toxicity profile. More recently, fluorodeoxyglucose-positron emission tomography (FDG-PET)-scan adapted therapy has emerged, which uses interim PET-scan results to direct treatment decisions; individuals classified as having high-risk disease based on interim PET-scan results may undergo treatment intensification; whereas, patients with lower-risk disease may be eligible for treatment de-escalation (e.g., initially ABVD for two cycles and then escalation to BEACOPP or de-escalation to AVD). Uptake of this strategy varies by region but is being adopted by an increasing number of treatment centres across Canada. HL is generally regarded as a curable disease; however, up to 30% of patients with advanced disease experience disease progression. The pCODR Clinical Guidance Panel (CGP) noted that there is still an unmet need in advanced

HL for more effective therapies with tolerable toxicity and the potential for long-term remission and cure.

Registered clinician input: adoption of BV in combination with AVD may be challenging as standards with PET-scan guided approaches have changed since initiation of ECHELON-1 trial

A total of two registered clinician inputs were provided: one from an individual oncologist from Cancer Care Ontario (CCO) and one joint input on behalf of five clinicians from Lymphoma Canada (LC). Both clinician inputs stated that the patient population in the reimbursement request aligns with the need in clinical practice. The clinicians from LC explained that BV in combination with AVD has proven to be better than ABVD without PET-based modification of therapy; however, the adoption of the drug may be challenging as standards with PET-adapted protocols have changed since the ECHELON-1 trial. The clinicians from LC believe that BV in combination with AVD would most likely be used as a complementary treatment, since there are multiple frontline options available. BV in combination with AVD may be a good option for some subgroups of patients such as those over 60 years of age or those with comorbidities, for whom the use of BEACOPP and ABVD may be limited due to toxicity issues. Both clinician inputs noted that neutropenia and peripheral neuropathy may be potential side effects of BV in combination with AVD. To prevent neutropenia, patients would likely receive G-CSF with BV in combination with AVD. The clinicians from LC further commented that patients with pre-existing neuropathy would be unlikely to receive BV in combination with AVD and would also likely have challenges with ABVD and BEACOPP. As BV in combination with AVD is a first-line treatment, the clinicians from LC noted that there could be implications in subsequent lines of therapies. Patients who have relapsed after BV in combination with AVD treatment would not likely receive BV-based treatments; however, BV alone can be considered for patients who did not experience significant toxicity after relapsing on BV in combination with AVD. The clinician from LC prefers the use of BV in combination with AVD over ABVD or BEACOPP. The clinician explained that although BEACOPP can be used initially, it is more commonly used in a PET-directed algorithm due to its toxicity profile. Even in a PET-directed algorithm, BV in combination with AVD will be used more than BEACOPP.

PATIENT-BASED VALUES

Experience of patients with HL: fatigue a key symptom; other symptoms include enlarged lymph nodes, drenching night sweats and itching

One patient input was provided by LC on BV for the treatment of previously untreated patients with stage IV HL, in combination with AVD. Fatigue was the most common HL symptom reported by patients, followed by enlarged lymph nodes, drenching night sweats, itching, persistent cough, unexplained weight loss, loss of appetite, trouble breathing, fever/chills, and chest pain. Anxiety/worry was reported as the most common symptom that had a significant impact on patients' QoL. When asked which aspect of their daily life was the most affected by HL, the majority of patients stated that HL had greatly affected their ability to work. The most common therapies for HL used by patients were ABVD, radiation therapy, and ASCT. Nausea, hair loss, and fatigue were reported by patients to be the most difficult to tolerate side effects of current treatments. Patients mentioned that current treatments also caused some financial burden due to absence from work/school, travel and parking costs, and costs of medication.

Patient values, experience on or expectations for treatment: disease control and remission; individualized treatment choices; and minimal/reduced side effects

Six patients reported having experience with BV in combination with AVD. The most common side effects of BV in combination with AVD reported were peripheral neuropathy, neutropenia, fatigue, and nausea/vomiting. The majority of patients noted that the side effects of the treatment had some impact on their overall QoL; however, when asked to what extent they are willing to tolerate the side effects of BV in combination with AVD, on a scale of 1 to 5 (1 = will not tolerate side effects; 5 = will tolerate significant side effects) five out of the six patients provided a rating of 4 or higher, indicating that patients are willing to tolerate side effects in favour of a cure or longer remission of the cancer. All six patients concluded that BV in combination with AVD has overall improved their health and wellbeing and that they would be willing to take the treatment again if their doctor recommended that it was the best treatment option for them. Overall, patients value new HL treatments that will result in disease control

or remission of the cancer, as well as the ability to choose personalized treatment options. Patients also emphasized minimal side effects or fewer side effects than current treatments as important outcomes.

ECONOMIC EVALUATION

The recommended dose of BV is 1.2 mg/kg of body weight, given intravenously, on days 1 and 15 of each 28-day cycle for up to six cycles, in combination with 25 mg/m^2 of doxorubicin, 6 mg/m^2 of vinblastine, and 375 mg/m^2 of dacarbazine. BV is supplied as 50 mg vials of lyophilized powder for intravenous infusion following reconstitution. The drug acquisition cost of BV is $4,840 per 50 mg vial. Assuming a mean body weight of 74 kg and a body surface area of 1.87 m^2 as per the ECHELON-1 trial and taking into account vial wastage, the cost of BV is estimated to be $19,360 over a 28-day cycle and $116,160 over six cycles. The BV in combination with AVD regimen is estimated to cost $21,579 over a 28-day cycle and $129,477 over six cycles.

The sponsor submitted a cost-utility analysis comparing BV in combination with AVD to ABVD in patients with previously untreated stage IV HL. The sponsor modelled the costs and quality-adjusted life-years (QALYs) over a lifetime time horizon (65 years) from a public health care payer perspective. The Markov model was characterized as health states primarily defined as frontline PFS; progression after frontline therapy and not receiving an ASCT; progression after frontline therapy and receipt of an ASCT; progression after ASCT; and death.

Patients entered the model in the frontline PFS health state where they received either BV in combination with AVD or ABVD. Patients who had not progressed after frontline treatment initiation were considered cured and did not progress. These patients remained in the frontline progression-free health state, whereas patients who progressed had a probability of undergoing ASCT. Patients who failed frontline therapy and did not receive ASCT remained in a no-ASCT state until their death. Patients who received ASCT were designated as either refractory from frontline therapy or relapsed. Patients designated as refractory had the additional option of receiving post-ASCT consolidation with BV due to being considered high-risk. All patients were assumed to have excess long-term mortality due to cytotoxic chemotherapy in addition to general population mortality, while patients on ABVD also faced an increased risk of mortality due to pulmonary toxicity, for the duration of the model time horizon. Baseline characteristics and the probability of progression following frontline treatment were derived from the ECHELON-1 trial. Investigator-assessed mPFS in stage IV patients with a median follow-up of 24.6 months was used to inform the base-case analysis for both treatment arms. mPFS was defined as the time to progression, death or receipt of an additional anticancer therapy for patients who were not in complete response after completion of frontline therapy. Mixture cure models were used to inform the transition probabilities and proportion of patients cured. These models produce a form of survival distribution where a proportion of the patients are assumed to be cured, while the rest of the population, considered the “uncured” proportion follow a separate mPFS survival distribution that is estimated and extrapolated using parametric survival analysis. Based on the best fitting mixture cure model, different frontline therapy cure proportions were observed for BV in combination with AVD and ABVD (proportion cured following frontline therapy: 79.2% versus 71.7%), but the best fitting model otherwise consisted of an identical survival distribution for uncured patients on both BV in combination with AVD and ABVD in the sponsor’s base case.

CADTH identified the following key limitations with the sponsor’s economic analysis:

- comparative treatment efficacy was based on the mPFS as assessed by investigators, which is at greater risk of bias compared to the same outcome as assessed by an IRF. This potentially overestimated the magnitude of clinical benefit with BV in combination with AVD compared to ABVD
- monthly costs of chemotherapy following frontline failure were likely overestimated, as the costs were inappropriately sourced and implemented within the model
- the sponsor assumed that the risk of mortality with pulmonary toxicity in patients on ABVD would endure for a patient’s lifetime, while the CGP noted this was likely to be for a far shorter duration (five years at most)
- the rate of use and efficacy of BV following ASCT, when BV has been administered as part of the initial frontline therapy, are uncertain

- the sponsor overestimated the proportion of patients on ABVD receiving G-CSF prophylaxis, thereby overestimating the costs associated with ABVD
- the sponsor did not consider BV in combination with AVD or ABVD within the context of PET-scan guided approaches. The cost-effectiveness of BV in combination with AVD in the context of PET adaptation, which is standard clinical practice in Canada, is unknown.

CADTH reanalyses included: use of treatment efficacy data (i.e., mPFS) as measured by an IRF instead of the investigator-assessed mPFS; correction of the monthly chemotherapy costs for patients in whom frontline therapy failed; adjustment of the duration of the effect of pulmonary toxicity on mortality risk with ABVD; and update of the proportion of patients on ABVD receiving G-CSF prophylaxis to better reflect the pivotal ECHELON-1 trial and Canadian clinical practice. In the CADTH base case, the incremental cost-effectiveness ratio for BV in combination with AVD compared with ABVD was $134,059 per QALY gained. The probability that BV in combination with AVD was cost-effective at a willingness-to-pay (WTP) threshold of $50,000 per QALY gained was 5%. Given the limitations with the implementation of chemotherapy costs after frontline therapy failure in the model and the limited data regarding the likely rate of use and efficacy of BV consolidation post-ASCT after BV has been used as part of the frontline regimen, the cost-effectiveness of BV in combination with AVD remains uncertain. CADTH scenario analyses suggest that the results are sensitive to chemotherapy costs after frontline therapy failure and to the rate and use of BV consolidation post-ASCT. A price reduction of at least 53% is required for BV to be considered cost-effective at a WTP threshold of $50,000 per QALY gained. The potential price reduction necessary for BV in combination with AVD to be cost-effective is uncertain, however, given the limitations with the analysis.

Due to the exclusion of PET-scan guided approaches within the sponsor's submission, the generalizability of these results to the use of BV in combination with AVD and ABVD within PET adaptation is uncertain, and as a result, the cost-effectiveness of BV in combination with AVD within the likely context of its use in Canadian clinical practice remains unknown.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Budget impact underestimated

The sponsor's assumed market uptake for BV in combination with AVD was underestimated according to the clinical experts consulted by CADTH, meaning that the total budget impact was underestimated. The CGP suggested a higher market uptake given the desirability of a regimen that excluded bleomycin. CADTH revised the market share as part of its reanalysis resulting in an estimated budget impact of $47,433,529 over three years. Due to the exclusion of PET-scan guided approaches within the sponsor's submission, the budget impact of BV in combination with AVD in settings where ABVD is used in the PET-adaptive context remains unknown. This would have an impact on the estimated market uptake of BV in combination with AVD, and the budget impact is highly sensitive to this parameter.

Factors related to currently funded treatments, the eligible patient population, implementation, and sequencing and priority of treatments are described in Appendix 1.

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)
Daryl Bell, Patient Member
Dr. Jennifer Bell, Bioethicist
Dr. Kelvin Chan, Oncologist
Dr. Michael Crump, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Dr. Christian Kollmannsberger, Oncologist
Dr. Christopher Longo, Health Economist
Cameron Lane, Patient Member
Valerie McDonald, Patient Member
Dr. Marianne Taylor, Oncologist
Dr. W. Dominika Wranik, Health Economist

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

- Dr. Maureen Trudeau, who did not vote due to her role as pERC Chair.
- Dr. Winson Cheung and Dr. Marianne Taylor, who did not vote as they were absent from the meeting.

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

- Dr. Maureen Trudeau, who did not vote due to her role as pERC Chair.
- Dr. Kelvin Chan, who did not vote as he was absent from the deliberations for this review.

Avoidance of conflicts of interest

All members of the pERC must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the CADTH website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of brentuximab vedotin (Adcetris), through their declarations, none of the 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 CADTH website. Please refer to the pCODR Guidance Reports for more detail on their content.

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

The information in this document is intended to help Canadian health care decision-makers, health care professionals, health systems leaders, and policy-makers make well-informed decisions and thereby improve the quality of health care services. While patients and others may access this document, the document is made available for informational purposes only and no representations or warranties are made with respect to its fitness for any particular purpose. The information in this document should not be used as a substitute for professional medical advice or as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision-making process. The Canadian Agency for Drugs and Technologies in Health (CADTH) does not endorse any

information, drugs, therapies, treatments, products, processes, or services.

While care has been taken to ensure that the information prepared by CADTH in this document is accurate, complete, and up-to-date as at the applicable date the material was first published by CADTH, CADTH does not make any guarantees to that effect. CADTH does not guarantee and is not responsible for the quality, currency, propriety, accuracy, or reasonableness of any statements, information, or conclusions contained in any third-party materials used in preparing this document. The views and opinions of third parties published in this document do not necessarily state or reflect those of CADTH.

CADTH is not responsible for any errors, omissions, injury, loss, or damage arising from or relating to the use (or misuse) of any information, statements, or conclusions contained in or implied by the contents of this document or any of the source materials.

This document may contain links to third-party websites. CADTH does not have control over the content of such sites. Use of third-party sites is governed by the third-party website owners' own terms and conditions set out for such sites. CADTH does not make any guarantee with respect to any information contained on such third-party sites and CADTH is not responsible for any injury, loss, or damage suffered as a result of using such third-party sites. CADTH has no responsibility for the collection, use, and disclosure of personal information by third-party sites.

Subject to the aforementioned limitations, the views expressed herein are those of CADTH and do not necessarily represent the views of Canada's federal, provincial, or territorial governments or any third-party supplier of information.

This document is prepared and intended for use in the context of the Canadian health care system. The use of this document outside of Canada is done so at the user's own risk.

This disclaimer and any questions or matters of any nature arising from or relating to the content or use (or misuse) of this document will be governed by and interpreted in accordance with the laws of the Province of Ontario and the laws of Canada applicable therein, and all proceedings shall be subject to the exclusive jurisdiction of the courts of the Province of Ontario, Canada.

Redactions: Confidential information in this document has been redacted at the request of the sponsor in accordance with the *pCODR Disclosure of Information Guidelines*.

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.

APPENDIX 1: CADTH PAN-CANADIAN ONCOLOGY DRUG REVIEW EXPERT REVIEW COMMITTEE RESPONSES TO PROVINCIAL ADVISORY GROUP IMPLEMENTATION QUESTIONS

PAG implementation questions	pERC Recommendation
Eligible patient population	
PAG is seeking guidance on whether the following patients would be eligible for treatment with BV in combination with AVD:	
• patients less than 18 years of age	• Patients < 18 years of age were excluded from the ECHELON-1 trial. pERC agreed with the CGP that there is currently insufficient evidence to make an informed recommendation on the use of BV in combination with AVD in patients < 18 years of age.
• patients with an ECOG performance score greater than 2	• pERC agreed with the CGP that the benefit for patients with ECOG PS > 2 cannot be formally concluded from the ECHELON-1 trial as these patients were excluded (trial eligibility criteria included ECOG PS of 0 to 2). However, it would be reasonable to offer BV in combination with AVD in situations in which the patients' poor performance status (i.e., ECOG PS 3 or greater) is affected by the underlying disease, based on clinical experience with BV and its manageable side-effect profile.
• patients with stage III HL (included in the trial) and stage IIB	• pERC noted that the CGP concluded that the trial results can be generalized to patients who have stage III disease as these patients were included in the ECHELON-1 trial. However, the HC approved indication and subsequently the reimbursement request are for only stage IV disease; therefore, pERC was unable to recommend BV in combination with AVD for patients with stage III disease. Upon reconsideration of the Initial Recommendation, pERC highlighted that the HC-approved indication was limited to patients with stage IV disease, although the sponsor's request to HC included the full trial population. HC highlighted uncertainties regarding efficacy (including inconsistency in observed mPFS benefit between stage III and IV subgroups, immature OS data, and use of surrogate end point); and increased SAEs in stage III patients compared to stage IV, which deemed the benefit-risk profile to be positive only for patients with stage IV disease. HC's final decision was based on the totality of evidence showing that the benefit of BV in combination with AVD was most substantial in patients with stage IV disease.
• nodular lymphocyte-predominant HL	• Patients with stage IIb disease were not included in the ECHELON-1 trial. pERC agreed with the CGP that some stage IIb patients (including those with disease that is not confined to the external beam radiation therapy (XRT) field or those with stage IIb disease and additional risk factors including extranodal sites and/or bulky mediastinal masses), would receive current standard of care protocols intended for advanced (stage III and IV) HL. However, the HC-approved indication and subsequently the reimbursement request are for only stage IV disease; therefore, pERC was unable to recommend BV in combination with AVD for patients with stage IIb disease.
• patients with cardiovascular conditions	

• patients with CNS involvement and PML symptoms.	• pERC agreed with the CGP that the trial results cannot be generalized to patients with nodular lymphocyte-predominant HL. Reed-Sternberg cells (that express CD30 antigens) are found only with classic HL. Nodular lymphocyte-predominant HL does not express CD30 and thus, it is not expected to respond to BV. • Patients with pre-existing cardiovascular disease were excluded from the trial. pERC noted that it would be reasonable to offer BV in combination with AVD to patients with stable cardiac disease. • Patients with cerebral or meningeal disease, including signs or symptoms of PML were excluded from the trial. pERC agreed with the CGP that there is insufficient evidence to generalize the results of the trial to these patients with CNS involvement and PML symptoms.
If recommended for reimbursement, PAG noted that patients who have initiated ABVD or BEACOPP would need to be addressed on a time-limited basis.	pERC agreed with the CGP that in the absence of sufficient evidence to guide this decision, it would be reasonable to offer BV in combination with AVD to patients who have initiated ABVD on a time-limited basis. However, pERC agreed with the CGP that patients who have initiated BEACOPP should not be offered BV in combination with AVD on a time-limited basis, as there is currently insufficient evidence on the safety and efficacy of BV in combination with AVD in patients who have started BEACOPP and have not progressed.
For patients who have started ABVD and experience tolerance issues with bleomycin, PAG questioned whether it would be appropriate to remove bleomycin and add in BV.	pERC agreed with the CGP that it would be reasonable to remove bleomycin and offer BV instead to patients who have started ABVD and experience tolerance issues with bleomycin.
PAG noted a potential for indication creep with BV for patients with earlier stages of disease and in other lines of therapy.	pERC agreed with the CGP that there are no data to support the generalizability of treatment benefit with BV in combination with AVD to patients with earlier stages of disease or other lines of therapy, which were not included in the ECHELON-1 trial.
With regard to combining BV with chemotherapies other than AVD, PAG is seeking guidance on: • substituting etoposide for patients unable to receive doxorubicin • combining BV with BEACOPP instead of AVD • using BV to replace bleomycin in BEACOPP.	pERC agreed with the CGP that the trial results cannot be generalized to BV in combination with chemotherapy regimens other than AVD. pERC agreed with the CGP that there is currently insufficient evidence regarding the safety profile of BV plus other combinations of drugs.
Implementation factors	
The recommended dose of BV is 1.2 mg/kg up to 120 mg on day 1 and 15 of a 28-day cycle. BV is given until disease progression, unacceptable toxicity, or a maximum of 6 cycles (24 weeks). PAG is seeking a clear definition of disease progression for the development of discontinuation criteria. In additional PAG is seeking information on what imaging is used and how often patients are scanned during and after treatment?	pERC agreed with the CGP that the ECHELON-1 trial criteria used for treatment discontinuation; that is, disease progression, unacceptable toxicity, or a maximum of 6 cycles (whichever occurs first), are reasonable and applicable to clinical practice. Currently, in clinical practice standard imaging requirements using CT (assessed using the Revised Response Criteria for Malignant Lymphoma) are used to confirm disease progression or relapse. Patients are typically scanned mid-course of treatment or after two cycles, and at the end of therapy. After treatment is complete, follow-up imaging tests are not common practice in

	Canada. Clinicians may, however, advise 1-2 imaging scans in the first 3-12 months after full completion of therapy.
The cost of supportive therapy (e.g., G-CSF) also needs to be considered in implementation as it will likely be required as primary prophylaxis and is typically not given with ABVD regimens. If BV in combination with AVD is recommended, should all patients receive primary prophylaxis with G-CSF, or are there subsets of patients that are at higher risk of febrile neutropenia that should only receive primary prophylaxis with G-CSF?	pERC supported the recommendation in the HC product monograph that primary prophylaxis with G-CSF is recommended beginning of cycle 1 for all patients who receive treatment with BV in combination with AVD. pERC agreed with the CGP that G-CSF may entail an additional cost. pERC acknowledged that the CGP cautioned that provincial funding of primary G-CSF is variable and not all patients may have access to it as a primary prophylaxis. Furthermore, some clinicians may prefer to use G-CSF as secondary prophylaxis and offer G-CSF as primary prophylaxis only in patients who receive BV in combination with AVD and are at high risk of febrile neutropenia.
Sequencing and priority of treatment	
What circumstances would drive the preference to prescribe BV in combination with AVD versus ABVD or BEACOPP?	pERC noted that since the inception of the ECHELON-1 trial, PET-scan guided approaches have emerged and are increasingly adopted across treatment centres in Canada. pERC was unable to determine how BV in combination with AVD compares with PET-scan guided approaches given the lack of comparative data. pERC discussed that there may be interprovincial and inter-clinician variability in choosing the optimal treatment. pERC agreed with some registered clinicians providing input to this submission that BV in combination with AVD may be used as a complementary treatment in case of tolerability or accessibility concerns with treatments that are currently available (i.e., ABVD, BEACOPP, and PET-scan guided approaches). pERC discussed that in rural areas PET scans are not routinely available and patients would have to travel several hours to reach a treatment centre that offers this procedure.
PAG is seeking guidance on possible sequencing of treatments after progression with BV including allogeneic stem cell transplant, immunotherapies, and potential re-treatment with BV.	pERC was unable to make an informed recommendation on the optimal sequencing of treatments for patients with stage IV HL who progress after treatment with BV in combination with AVD. pERC noted that it did not review evidence to inform sequencing of treatments after progression with BV. However, pERC recognized that provinces will need to address this issue upon implementation of reimbursement of BV in combination with AVD and noted that a national approach to developing clinical practice guidelines addressing sequencing of treatments would be of value.
Evidence for continuing BV as a single drug for high-risk patients after completion of BV in combination with AVD.	pERC agreed with the CGP that there is insufficient evidence to make a recommendation regarding continuing BV as a single drug for high-risk patients after completion of BV in combination with AVD.

ABVD = doxorubicin, bleomycin, vinblastine, and dacarbazine; AVD = doxorubicin, vinblastine, and dacarbazine; BEACOPP = bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; BV = brentuximab vedotin; CGP = CADTH Clinical Guidance Panel; CNS = central nervous system; CT = computerized tomography; ECOG = Eastern Cooperative Oncology Group; G-CSF = granulocyte colony-stimulating factor; HC = Health Canada; HL = Hodgkin lymphoma; PAG = Provincial Advisory Group; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; PML = progressive multifocal leukoencephalopathy.