Canada's Drug and Health Technology Agency

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

Brentuximab vedotin (Adcetris)

Indication: Brentuximab vedotin in combination with doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide in previously untreated high-risk HL in the pediatric population. Brentuximab vedotin in combination with doxorubicin, vinblastine, and dacarbazine for the treatment of previously untreated patients with advanced stage HL.

Sponsor: BC Cancer Agency and Pediatric Oncology Group of Ontario

Recommendation: Reimburse with Conditions

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Recommendation

The pCODR Expert Review Committee (pERC) recommends that brentuximab vedotin be reimbursed for the treatment of previously untreated patients with advanced stage Hodgkin lymphoma (HL) only if the conditions listed in Table 1 are met.

This recommendation supersedes the pERC recommendation for brentuximab vedotin for the treatment of previously untreated patients with Stage IV HL in combination with doxorubicin, vinblastine, and dacarbazine (AVD) dated December 3, 2020.

Rationale for the Recommendation

One phase III, multicentre randomized controlled trial (RCT; ECHELON-1) demonstrated that treatment with brentuximab vedotin in combination with doxorubicin, vinblastine, and dacarbazine (BV + AVD) resulted in a benefit in overall survival (OS), modified progression-free survival (mPFS), and progression-free survival (PFS) per investigator compared to doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) in previously untreated adult patients who were diagnosed with advanced stage (i.e. Ann Arbor stage III and IV) classical HL. As of the data cut-off date of March 11, 2023 with a median follow-up of approximately 88 months, the hazard ratio (HR) was 0.61 (95% confidence interval [CI]: 0.414 to 0.892) and there was a 3% absolute reduction in number of OS events between the BV + AVD group and the ABVD group, favouring BV + AVD, in the intention-to-treat (ITT) population. Results for mPFS per independent review facility (data cut-off date: April 20, 2017; HR: 0.770; 95% CI: 0.603 to 0.982) and PFS per investigator-assessment (data cut-off date: June 1, 2021; HR for PFS: 0.678; 95% CI: 0.532 to 0.863;) in the ITT population also favoured the BV + AVD group.

Another phase III, multicentre RCT (AHOD1331) demonstrated that brentuximab vedotin in combination with doxorubicin, vincristine, etoposide, prednisone, cyclophosphamide (BV + AVEPC) provides a clinically meaningful benefit in event-free survival (EFS) compared to doxorubicin, bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide (ABVE-PC) in patients aged ≥ 2 years and < 22 years with high-risk classical HL defined as Ann Arbor stage IIB with bulk tumour, stage IIIB, stage IVA, and stage IVB HL. After a median follow-up time of 42.1 months, the proportion of patients who had not experienced an EFS event (disease progression or relapse, second malignancy, or death) and thus were censored for the 3-year EFS analysis was 92.1% (95% CI: 88.4 to 94.7) in the BV + AVEPC group and 82.5% (95% CI: 77.4 to 86.5) in the ABVE-PC group. The HR for 3-year EFS was 0.41 (95% CI: 0.25 to 0.67, P < 0.001) favouring the BV + AVEPC group.

Patients identified a need for new treatments for HL that control disease symptoms, prolong remission, prolong survival, and improve quality of life. In addition, clinicians indicated there is a need to avoid further therapies and late effects in the pediatric population. Given the totality of the evidence, pERC concluded that brentuximab vedotin met some of the needs identified by patients because it prolongs disease remission, prolongs survival, and may delay the need for further therapies.

Using the sponsor submitted price for brentuximab vedotin and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for BV + AVD was $115,865 per quality-adjusted life-year (QALY) gained compared with ABVD in adults. At this ICER, BV + AVD is not cost-effective at a $50,000 per QALY gained willingness to pay (WTP) threshold for previously untreated adult patients with advanced stage HL. A price reduction is required for BV + AVD to be considered cost-effective at a $50,000 per QALY gained threshold.

As the manufacturer used data from ECHELON-1 to inform clinical effectiveness, and since the trial data excluded pediatric patients, the results of the economic evaluation represent cost-effectiveness of BV + AVD for the treatment of previously untreated adult patients with advanced stage HL. As such, the clinical and cost effectiveness of BV + AVD compared with most relevant comparators for those under 18 years of age is unknown. Additionally, as CADTH was unable to incorporate data from the AHOD1331 trial into the manufacturer's model, CADTH was unable to estimate the cost-effectiveness of BV + AVEPC compared with ABVE-PC.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Brentuximab vedotin should only be initiated in previously untreated patients who meet either of the following: 1.1. Adults aged 18 years or older with advanced stage classical HL, defined as stage III and IV according to the Ann Arbor staging system 1.2. Children and adolescents aged 2 years or older with high-risk HL, defined as stage IIB with bulk tumour or stage IIIB, IVA, or IVB according to the Ann Arbor staging system	Evidence from the ECHELON-1 trial demonstrated that treatment with BV + AVD has a beneficial effect compared to ABVD in adult patients with previously untreated advanced stage (i.e., Ann Arbor stage III or stage IV) HL. Evidence from the AHOD1331 trial demonstrated that treatment with BV + AVPEC has a beneficial effect on EFS compared to ABVE-PC in patients aged ≥ 2 years and < 22 years who were previously untreated for high-risk classical HL (i.e., Ann Arbor stage IIB with bulk tumour, stage IIIB, stage IVA, stage IVB).	—
2. Patients must have good performance status.	The ECHELON-1 trial included patients with an ECOG PS of 0 to 2.	—
3. Brentuximab vedotin should not be used in patients who have any of the following: 3.1. Nodular lymphocyte-predominant HL 3.2. Severe sensory or motor peripheral neuropathy 3.3. Cerebral or meningeal disease 3.4. Neurological disease affecting activities of daily living	Patients with nodular lymphocyte predominant HL; cerebral or meningeal disease, including signs or symptoms of progressive multifocal leukoencephalopathy; neurologic disease requiring medication or compromising normal activities of daily living; and peripheral sensory or motor neuropathy were excluded from the ECHELON-1 trial.	—
Discontinuation		
4. Treatment should be continued until disease progression, unacceptable toxicity, or completion of the maximum number of treatment cycles, whichever comes first.	BV + AVD was given for 6 cycles in the ECHELON-1 trial. Patients in the ECHELON-1 trial discontinued treatment if they experienced progressive disease, unsatisfactory therapeutic response, or unacceptable toxicity. In the AHOD1331 trial, BV + AVEPC was given for 5 cycles unless patients met criteria for removal from protocol therapy such as progressive disease, physician's determination, or development of a second malignancy.	In adult patients, treatment with BV + AVD should be for a maximum of 6 cycles. In pediatric patients, treatment with BV + AVEPC should be for a maximum of 5 cycles.
Prescribing		
5. BV + AVD should be prescribed by a clinician with expertise and	This is to ensure brentuximab vedotin is prescribed only for appropriate patients	—

Reimbursement condition	Reason	Implementation guidance
experience in the treatment of HL. In pediatric patients, BV + AVPEC should be prescribed by a clinician with expertise in pediatric oncology.	and adverse effects are managed in an optimized and timely manner.	
6. Brentuximab vedotin should not be used in combination with chemotherapy drugs other than AVD in adults or AVPEC in pediatric patients.	The ECHELON-1 trial provided evidence for BV + AVD and the AHOD1331 trial provided evidence for BV + AVEPC. pERC did not review evidence supporting the use of brentuximab vedotin in combination with other chemotherapy drugs.	—
Pricing		
7. A reduction in price	In a population of previously untreated adult patients with advanced stage HL, the ICER for BV + AVD is $115,865 per QALY gained when compared with ABVD. A 55% reduction in the price of BV would be required for BV + AVD to achieve an ICER of $50,000 per QALY compared to ABVD. In a population of pediatric patients with advanced stage HL, the cost-effectiveness of BV is unknown.	—

AVD = doxorubicin, vinblastine, and dacarbazine; AVEPC = doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide; BV + ABVE-PC = brentuximab vedotin in combination with doxorubicin, bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide; BV + AVD = brentuximab vedotin in combination with doxorubicin, vinblastine, and dacarbazine; HL = Hodgkin lymphoma; ICER = incremental cost-effectiveness ratio; QALY = quality adjusted life-year

Discussion Points

- **Subgroup analyses by disease stage:** pERC recognized the uncertainty around the magnitude of benefit in the stage III population versus the stage IV population given the ECHELON-1 trial was not stratified or designed to detect treatment effects within **s**ubgroups according to stage. Potentially small treatment effects (and uncertain benefit to risk ratio) were identified by Health Canada in 2019 restricting the approved indication to stage IV disease. pERC discussed that although subgroup analyses of the OS and mPFS results signaled that BV + AVD might be more effective in patients with stage IV classical HL than those with stage III classical HL, conclusions regarding subgroup differences between stage III vs. stage IV patients are uncertain due to limitations of trial design and subgroup analyses. The consulted clinical experts highlighted that the approach to treatment, especially with their experience using ABVD, is to treat stage III and stage IV classical HL in the same manner. The manufacturer's submitted model structure did not allow for the exploration of the treatment effect of BV+AVD by disease stage. As such, the cost-effectiveness of BV+AVD by disease stage is unknown.
- **Health-related quality of life:** Patient group input highlighted the importance of improved HRQoL. In the ECHELON-1 trial, HRQoL outcome measures (EORTC-QLQ-C30 and EQ-5D-3L VAS) showed improvements in both treatment groups and similar scores between the BV + AVD and ABVD groups. However, interpretation of these results is complicated by the analyses being exploratory and no formal between-group comparisons were done for the EQ-5D-3L VAS. Results for HRQoL outcomes were not reported in the publication for the AHOD1331 trial.
- **Pediatric population:** pERC noted that there remains an evidence gap with respect to the clinical efficacy and safety of BV+AVD in the pediatric population as all participants in the ECHELON-1 trial were required to be ≥ 18 years of age. Furthermore, pERC acknowledged input from clinician groups and clinical experts that brentuximab vedotin would be used in combination with a pediatric chemotherapy backbone (i.e., AVEPC) instead of AVD in the pediatric patient population. To address the unmet needs in the pediatric patient population, pERC considered evidence from the AHOD1331 trial, which

demonstrated that BV + AVEPC is more effective than ABVE-PC for EFS in pediatric patients with high-risk classical HL. The manufacturer model did not assess the cost-effectiveness of BV in a pediatric population. Given all participants of ECHELON-1 (used to populate the clinical effects of BV + AVD in the economic model) were required to be ≥ 18 years of age, the clinical- and cost-effectiveness of BV + AVD in pediatric patients is unknown. CADTH was unable to incorporate data from the AHOD1331 trial into the manufacturer's model. As such, the cost-effectiveness of BV + AVEPC is unknown.

- **Adverse events:** The safety profile of BV + AVD is consistent with the known AEs for the individual components of the regimen, but it was notable that more patients treated with BV + AVD experienced SAEs than in the ABVD group of the ECHELON-1 trial. pERC acknowledged that BV + AVD had notable side effects such as neuropathy and risk of febrile neutropenia, however, these were manageable, and no significant detriment to quality of life was observed in the ECHELON-1 trial. pERC noted that later in the trial, primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) was used in 83 patients in the BV + AVD arm and 43 patients in the ABVD arm to prevent neutropenia or febrile neutropenia. This resulted in lower rates of neutropenia and febrile neutropenia compared to those who had not received G-CSF prophylaxis, though these rates remained higher than the rates in patients in the ABVD group who also received G-CSF prophylaxis. However, pERC noted that fewer patients in the BV + AVD arm experienced pulmonary-related toxicity than those in the ABVD arm.
- **Gaps in the evidence:** pERC acknowledged that PET-adapted BEACOPP and PET-adapted ABVD are relevant comparators since they are commonly used as first-line treatments for patients with advanced HL in Canada. However, pERC could not draw conclusions regarding the relative efficacy and safety of BV + AVD compared with PET-scan guided approaches given the lack of comparative data.
- **Budget impact is uncertain:** In CADTH's base case estimate of the budget impact of introducing BV, pediatric patients were included and it was assumed that the chemotherapy backbone and comparator treatment they will receive is identical to adults, which is contradictory to feedback provided by clinical experts for this review. CADTH did not address this in reanalyses as it is beyond the scope of a CADTH review. The results of a CADTH scenario analysis estimated that there are approximately 13 pediatric patients per year in the pan Canadian BIA (39 pediatric patients over 3 years). ,Tthe 28-day cycle costs of treating pediatric patients with BV + AVEPC is $21,110, or $105,551 for 5 cycles of treatment (). As such, the cost of treating pediatric HL patients with BV + AVEPC would be approximately $1,372,165 per year (assuming 13 patients are treated per year).

Background

HL is a B-cell malignancy that originates in the lymphocytes. Classical HL accounts for 95% of all HL cases. The estimated incidence in Canada in 2022 was 2.6 cases per 100,000. Based on 2018 Canadian Cancer Statistics, which reported cancer incidence by stage, approximately 23.3% of Canadian patients presenting with HL have stage III disease and 22.7% have stage IV disease. Childhood HL represents 6% of all cancers and has an incidence rate of 12 cases per million (1.2 cases per 100,000) per year in the 0 to14 year age group. In 2019, 25 children in Canada in this age group were diagnosed with HL.

The goal of therapy in patients with advanced HL is curative. The clinical experts consulted by the review team noted that patients with advanced HL are treated the same, regardless of stage. Current first-line treatment regimens for adult patients with advanced stage HL rely on chemotherapy. For adult patients with stage IV HL, the preferred regimen is BV + AVD. For patients with advanced HL, treatment approaches also include doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) for up to 6 cycles with positron emission tomography response after 2 cycles of chemotherapy (PET2)-directed treatment adaptation, as well as based on upfront PET2-driven treatment adaptation with bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP). For pediatric patients, the clinical experts consulted by the review team also noted that most clinical centers in Canada use doxorubicin, bleomycin, vincristine sulfate, etoposide phosphate, prednisone, and cyclophosphamide (ABVE-PC) for 5 cycles with radiation therapy determined by PET2, while relatively fewer centers use vincristine, etoposide, prednisone, and doxorubicin - cyclophosphamide, vincristine, prednisone, and dacarbazine (OEPA-COPDAC).

Brentuximab vedotin has been approved by Health Canada for the treatment of previously untreated patients with Stage IV HL, in combination with doxorubicin, vinblastine, and dacarbazine. Brentuximab vedotin is an antibody-drug conjugate. Brentuximab vedotin is available as lyophilized powder for reconstitution and the dosage recommended in the product monograph for previously untreated Stage IV HL is 1.2 mg/kg up to a maximum of 120 mg in combination with AVD as an IV infusion over 30 minutes, administered every 2 weeks for a maximum of 12 doses (i.e., administered on Days 1 and 15 of each 28-day cycle up to a maximum of 6 cycles) or until disease progression or unacceptable toxicity.

Submission History

BV + AVD was previously reviewed by CADTH and received a recommendation to reimburse with conditions for the treatment of previously untreated patients with Stage IV HL from the pERC (issued on December 3, 2020). The original CADTH review of BV + AVD included the ECHELON-1 trial. pERC made this recommendation because it was satisfied that BV + 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 in the ITT 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. In the 2020 recommendation, 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 approved indication was limited to patients with stage IV. 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.

In the present review, pERC considered the following unlabeled indications:

- BV + AVD for the treatment of previously untreated patients with advanced stage HL (an expansion of the labelled indication for stage IV disease to also include stage III)
- BV + AVEPC in previously untreated high-risk HL in the pediatric population.

This tumour group submission is based on updated data from the ECHELON-1 trial and a new trial conducted in the pediatric population, the AHOD1331 trial. Of note, this review is based on a previous sponsor-initiated submission (Project Number PC0311-000) that was withdrawn.

Sources of Information Used by the Committee

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

- a review of 1 phase III, open-label RCT (ECHELON-1) in previously untreated adult patients (≥ 18 years of age) who were diagnosed with advanced stage (i.e., Ann Arbor stage III and IV) classical HL and 1 phase III, open-label RCT in patients aged ≥ 2 years and < 22 years who were previously untreated for high-risk classical HL (i.e., Ann Arbor stage IIB with bulk tumour, stage IIIB, stage IVA, stage IVB)
- patients' perspectives gathered by 1 patient group, Lymphoma Canada (LC)
- input from public drug plans and cancer agencies that participate in the CADTH review process
- 3 clinical specialists with expertise diagnosing and treating patients with HL
- input from 2 clinician groups, OH-CCO Hematology Cancer Drug Advisory Committee and POGO
- a review of the pharmacoeconomic model in adults only and report submitted by the manufacturer

Stakeholder Perspectives

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

Patient Input

One patient group, LC, provided input for BV for the treatment of previously untreated patients with advanced stage HL, in combination with AVD. Patient input was gathered from an online anonymous patient survey from March 14 to May 2, 2023. In total 26 responses were gathered, and 3 of these patients reported receiving BV + AVD treatment.

Patients were asked questions regarding the physical and psychosocial symptoms experienced at the time of diagnosis, current quality of life, and how these symptoms impacted their daily activities. At the time of their lymphoma diagnosis, most of the patients reported fatigue (79%) as the most impactful symptom (5 out of 5), followed by enlarged lymph nodes (58%), shortness of breath (63%), and weight loss (47%). In addition, 74% of patients reported experiencing anxiety or worry, 68% stressing about their diagnosis, 63% difficulty in sleeping, and 58% fearing progression of their lymphoma. Regarding physical symptoms that currently impact their quality of life, fatigue (29%) and headaches (14%) were identified as most significant factors having a negative impact of quality of life out of 7 responses. The most impactful psychosocial factors impacting the patients' current quality of life were the stress of having cancer (71%), fear of progression (71%), anxiety or worry (71%), difficulty sleeping (43%), problems concentrating (43%), and inability to attend work or school (43%).

Among the surveyed patients, 3 patients indicated receiving ABVD in the frontline setting, 2 were treated with other forms of chemotherapy, and 1 was treated with cyclophosphamide, doxorubicin, prednisone, rituximab, and vincristine. While evaluating the importance of outcomes of new treatments, patients from the survey placed importance on the need for a novel lymphoma therapy to control disease symptoms, longer disease remission, allowing to live longer and improved quality of life.

While describing the experience with the treatment under review, one of the 3 patients that had received BV + AVD indicated they have been in-remission for 6 months up to a year, another in remission longer than a year, and the other patient is in post treatment (not sure about remission status). Side effects from the BV + AVD treatment reported by patients were fatigue (n = 3), neutropenia (n = 2), constipation (n = 2), joint or muscle pain (n = 2), low platelet count (n = 1), decreased appetite (n = 1), low blood pressure (n = 1), and decreased appetite (n = 1). Moreover, 2 patients reported experiencing financial setbacks due to absence from work and one due to cost of other medications. One of these patients mentioned having a poor experience with BV, and the other two rated their experience as very good.

Clinician input

Input from clinical experts consulted by the review team

The clinical experts consulted by the review team noted that improving the proportion of patients cured with first-line treatment is an important unmet need for patients with advanced stage HL. The clinical experts also highlighted the need to reduce treatment failure, prevent disease progression or relapse, and avoid late side effects (e.g., secondary malignancies, cardiac and pulmonary late effects) and further therapies that are toxic (e.g., autologous stem cell transplantation [ASCT]), especially for patients diagnosed with advance stage HL at younger age and for older patients who have poor tolerance to treatment.

The clinical experts noted that BV + AVD is considered as frontline therapy for advanced HL. The clinical experts noted that, at the time of the review, BV + AVD had been approved for the treatment of previously untreated patients with stage IV HL only, and the use of BV + AVD in patients with stage III classical HL would cause a shift in the current treatment paradigm for those patients. The clinical experts indicated that in pediatric patients, BV would be used in combination with a different chemotherapy backbone, namely the one investigated in a phase III randomized controlled trial in pediatric patients (AHOD1331[12]) (i.e., BV in combination with doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide [BV + AVEPC]). Trials of BV + AVD in pediatric patients have not been completed at the time of this review.[13]

The clinical experts noted that any previously untreated adult patients with stage III or IV classical HL who meet the eligibility criteria of ECHELON-1 trial are best suited for the use of BV + AVD. The clinical experts indicated that pediatric patients with advanced stage classical HL could also be eligible for BV in combination with chemotherapy, and the eligibility for therapy should be determined by the treating physician or using the eligibility criteria of the AHOD1331 trial.

The clinical experts noted that positron emission tomography (PET) scans, typically PET2 (after 2 cycles of chemotherapy) and a PET scan after all 6 cycles (end-of-treatment), are used for response assessment. In patients who have complete response, follow-up visits take place every 3 to 4 months for 2 years, then typically every 6 months for 3 more years. Patients with a partial response may undergo radiation therapy, and patients with refractory disease would undergo further investigations (e.g., biopsy) and treatment with a 2nd-line regimen. The clinical expert specializing in pediatrics noted that outcomes used in clinical practice to assess treatment response are generally aligned with outcomes typically used in adult patients.. The clinical experts noted that overall survival (OS) is the most clinically meaningful outcome to assess the efficacy of BV in combination with chemotherapy in patients with advanced stage HL, and progression-free survival (PFS) is an important outcome. In pediatric patients, event-free survival (EFS) is also important.

The clinical experts agreed that overall, discontinuation of BV + AVD is uncommon because unacceptable toxicity or refractory HL is not common. The clinical experts highlighted several situations in which BV + AVD can be discontinued, including 1) treatment is complete; 2) there is clear progression of disease; 3) there is an unacceptable adverse event (AE).

The clinical experts noted that diagnosis of the disease in adult patients must be made by an experienced pathologist. Selection of patients for BV + AVD should be done by a hemato-oncologist who has experience with treating HL. Treatment can be delivered in the specialty clinics of non-academic centers. The clinical expert specializing in pediatrics noted that all pediatric oncology patients are cared for by pediatric oncology teams at a tertiary care center. Some aspects of care may be provided at satellite centers after diagnostic and management decisions are made.

Clinician group input

Clinician group input on the review of brentuximab vedotin was received from OH-CCO Hematology Cancer Drug Advisory Committee and POGO. A total of 6 clinicians provided input on behalf of OH-CCO. POGO is a collaboration of Ontario's 5 specialized childhood cancer centres. The input collected from POGO was prepared in a consultative manner, where one clinician discussed the indication with other members of the submission panel and sought input from POGO's Therapeutic and Technology Advisory Committee, based on which the final submission was prepared.

OH-CCO highlighted the need to improve outcomes with first-line therapy, so that second-line therapy can be avoided. The group noted that patients with stage III and IV disease would be best suited for current treatment. The group indicated that typical

lymphoma response measures including PET scan are used in clinical practice to assess patients' response to treatment. They noted they would discontinue treatment with BV + AVD in cases of significant toxicities, or disease progression.

POGO noted that while there are a variety of chemotherapy and radiation approaches as options for the standard of care, these vary by region and between pediatric and adult focused practitioners in Canada. POGO reported that historically, the ABVD chemotherapy backbone used with BV in adult patients has not been used by pediatric oncologists to treat pediatric patients due to concern of higher anthracycline (doxorubicin) and bleomycin exposure, and the known dose-dependent cardiac and pulmonary toxicities. POGO noted that BV has been studied and used in combination with another chemotherapy regimen (AVEPC) in patients aged 2 to 21 years with previously untreated high-risk Hodgkin lymphoma.[14] POGO indicated that this alternate chemotherapy backbone is more commonly used in the pediatric setting, and BV-AVEPC has become standard care for high-risk pediatric patients in Ontario. Regarding treatment goals in pediatric patients with HL, POGO highlighted the need to avoid disease recurrence to minimize potential late effects from subsequent chemotherapies and autologous stem cell transplant received at relapse, and the associated impact on health-related quality of life. While describing the outcomes used to determine whether a pediatric patient is responding to treatment for HL, the POGO group emphasized the importance of OS and EFS, considering the higher chance of experiencing late effects of therapy after treatment among the younger patient population. Similar to OH-COO, POGO suggested treatment be discontinued at disease progression.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions from the Drug Programs

Implementation issues	Response
Relevant comparators	
ECHELON-1 trial included ABVD as comparator which is the current standard frontline treatment for HL. An alternative regimen for young and healthy patients for whom the infertility implications are acceptable is BEACOPP which can be given in fixed or escalated dosing. PET-CT scan guides treatment (i.e., number of cycles, change in therapy between ABVD and BEACOPP). In some provinces, CVPP can be given to patients with contraindications to anthracyclines and/or bleomycin. The ECHELON-1 trial compared BV + AVD to ABVD. PAG is also seeking comparison of BV with PET-adapted BEACOPP and ABVD.	For adult patients in Canada, the clinical experts consulted by CADTH noted that escalated BEACOPP and PET-adapted BEACOPP are only used in a few centers, and CVPP is not commonly used. For pediatric patients, relevant comparators to BV in combination with chemotherapy included ABVD, ABVE-PC or OEPA/COPDAC. pERC agreed that PET-adapted BEACOPP and PET-adapted ABVD are relevant comparators. However, pERC noted that only evidence comparing BV + AVD to ABVD from the ECHELON-1 trial and evidence comparing BV + AVEPC to ABVE-PC from the AHOD1331 trial was submitted for this review. Therefore, pERC could not comment on how BV + AVD compares to PET-adapted BEACOPP and PET-adapted ABVD.
Considerations for initiation of therapy	
Are there disease-specific features or prognostic features that would influence choice of therapy between PET guided BEACOPP/ABVD and BV + AVD?	The clinical experts consulted by CADTH noted that the toxicity of BEACOPP and the improvement in OS with BV + AVD make BV + AVD a preferred treatment regimen in adult patients. Currently in clinical practice, the clinical experts favor BV + AVD over PET guided ABVD/BEACOPP in adult patients with stage IV HL. The clinical experts also noted that if BV + AVD is approved for adult patients with stage III HL, BV + AVD will be preferred in this patient population as well. pERC discussed that there may be interprovincial and inter-clinician variability in choosing the optimal treatment. pERC did

Implementation issues	Response
	not identify any disease-specific features or prognostic features that would influence choice of therapy since this is a complex discussion between the treating clinician and individual patient based on multiple factors, including age, toxicity profile and patient values.
The indication requested for review is advanced stage HL. Is advanced stage definition limited to stage III and IV? What staging system should be used (Lugano or Ann Arbor)?	The clinical experts consulted by CADTH noted that advanced stage HL in adults refers to stage III and IV HL according to the Ann Arbor staging system. The clinical expert specialized in pediatric oncology noted that in current clinical practice, pediatric patients with HL are usually classified into low, intermediate, and high-risk groups, and the high-risk group is generally considered equivalent to the advanced stage classical HL in adults. The clinical experts reported that the Children's Oncology Group trial (AHOD1331[10]) defined pediatric patients with high-risk/advanced stage HL as stage IIB with bulk tumour, stage III with B symptoms (stage IIIB), and stage IV with or without B symptoms (stage IVA and stage IVB) determined by Ann Arbor staging system. The clinical experts consulted by CADTH noted that Lugano criteria are criteria which allow one not only to stage the lymphoma but also to assess response. In the Lugano criteria, staging is performed using the Ann Arbor staging system. pERC agreed with defining advanced stage disease in alignment with the ECHELON-1 trial criteria for adults and the AHOD1331 trial criteria for the pediatric population.
Per the current provisional funding algorithm for adult patients who relapse would be eligible for BV re-treatment if relapse occurs more than 12 months after completion of prior BV therapy with at least 6 months of response. Is pERC in agreement with this guidance which was informed by the pERC recommendation for BV + AVD in stage IV HL?	The clinical experts consulted by CADTH noted that in Ontario and Quebec, BV cannot be given unless a patient who relapsed has had a transplant, in which BV can be used as maintenance or if the patient has relapsed after the transplant. pERC agreed with the guidance informed by the 2020 pERC recommendation for BV + AVD in stage IV HL.
Should BV + AVD be available to patients: • With ECOG PS score greater than 2 • Nodular lymphocyte-predominant HL (no CD30 expression) • Stage IIB disease at high risk • With CNS involvement • With PML symptoms	The clinical experts consulted by CADTH noted that BV + AVD should be available to patients: • With ECOG PS score greater than 2 • Stage IIB disease at high risk (in children, not in adults) • With CNS involvement The clinical experts noted that CNS involvement is rare in patients with advanced HL. Reimbursement criteria regarding performance status and disease stage are outlined in Table 1. pERC agreed with the clinical experts that patients with CNS involved could be eligible. The clinical experts indicated that PML is a rare condition in these patients and fatal. They indicated they would not treat patients who had PML and HL for their lymphoma with BV + AVD. pERC agreed with the clinical experts. Consider adding the following (taken from CADTH review of BV for stage IV).

Implementation issues	Response
	pERC agreed with the clinical experts 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.
Considerations for discontinuation of therapy	
Consistency with discontinuation criteria associated with other drugs reviewed by CADTH in the same therapeutic space Treatment with BV + AVD should continue until disease progression, unacceptable toxicity or until a maximum of 6 cycles, whichever comes first.	pERC and the clinical experts consulted by CADTH agreed with the current discontinuation criteria for BV + AVD in adults. pERC noted that in the pediatric population, BV + AVEPC should continue until disease progression, unacceptable toxicity or until a maximum of 5 cycles, whichever comes first.
Considerations for prescribing of therapy	
For patients unable to receive doxorubicin, can etoposide be substituted (i.e., BV with etoposide/bleomycin/vinblastine/dacarbazine)?	The clinical experts consulted by CADTH do not agree with the substitution. pERC also did not agree with the substitution.
Consider alignment with prescribing criteria for BV + AVD in stage IV disease	This is a comment from the drug plans to inform pERC deliberations.
Generalizability	
Should adult patients who recently initiated ABVD or BEACOPP be eligible to switch to BV + AVD? PAG noted that the previous review for BV + AVD for stage IV disease the CGP indicated it would be reasonable to switch patients initiated on ABVD to BV + AVD on a time limited basis. CGP noted that patients initiated on BEACOPP should not be offered BV + AVD on a time limited basis.	The clinical experts who treat adult patients indicated there should be an option to switch on a time limited basis. pERC agreed with the clinical experts. The clinical expert who treats pediatric patients noted that such situation would not likely occur when treating pediatric patients as the pediatric setting is different from the adult setting. pERC noted that it may be reasonable for pediatric patients to have the option to switch to BV + AVEPC on a time limited basis as well.
Funding algorithm	
Existing algorithm to be updated to include use of BV + AVD for stage III disease if recommended for reimbursement	This is a comment from the drug plans to inform pERC deliberations.
Care provision issues	
Primary prophylaxis with G-CSF is typically prescribed with BV + AVD and is associated with additional cost.	This is a comment from the drug plans to inform pERC deliberations.
Is it appropriate for patients initiated on ABVD who experience treatment-related adverse effects to be switched to BV + AVD to complete maximum of 6 cycles?	The clinical experts consulted by CADTH do not consider the switch appropriate. pERC agreed with the clinical experts.
Can BV be combined with any other regimens other than AVD (i.e., substituting etoposide in patients unable to receive doxorubicin).	pERC noted that the scope this review is limited to BV + AVD for the treatment of previously untreated patients with advanced stage HL and BV + AVEPC in previously untreated high-risk HL in the pediatric population. Furthermore, only evidence comparing BV + AVD to ABVD in adult patients (ECHELON-1 trial) and evidence comparing BV + AVEPC to ABVE-PC in pediatric patients (AHOD1331 trial) was submitted. Therefore, pERC could not comment on combining BV with other regimens.

ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine; ABVE-PC = adriamycin, bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide; AVPEC = doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide; BEACOPP = bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; BV + AVD = brentuximab vedotin in combination with doxorubicin, vinblastine, dacarbazine; CNS = central nerve system; COPDAC = cyclophosphamide, vincristine, prednisone, and dacarbazine; CT = computerized tomography; CVPP = cyclophosphamide, vinblastine, procarbazine, and prednisone; ECOG PS = Eastern Cooperative Oncology Group performance status; G-CSF = granulocyte colony-stimulating factor; HL = Hodgkin lymphoma; OPEA = vincristine, etoposide, prednisone, and doxorubicin; OS =overall survival ; PET = positron emission tomography; PML = progressive multifocal leukoencephalopathy.

Clinical Evidence

Pivotal Studies and RCT Evidence

Description of studies

One phase III, open-label, randomized, active-controlled, superiority trial (ECHELON-1, N = 1,334) was identified from a systematic literature review conducted by the manufacturer.[15,16] The primary objective of the ECHELON-1 trial was to determine the efficacy of BV + AVD relative to ABVD measured by mPFS. The key secondary objective was to compare OS between BV + AVD and ABVD. The ECHELON-1 trial is ongoing. Data from the data cut-off date: April 20, 2017 and June 1, 2021 were assessed for this review. New data from a descriptive analysis of OS conducted in response to a request for supplementary information from the European Medicines Agency (EMA) with a data cut-off date of March 11, 2023 was also included in this report.

Participants eligible to be included in the ECHELON-1 trial were previously untreated adult patients with histologically confirmed advanced stage classical HL, consisting of stage III and stage IV patients determined by the Ann Arbor classification system. Patients with nodular lymphocyte-predominant HL and those with sensory or motor peripheral neuropathy were excluded. The median age of enrolled patients was 36 years (range: 18 to 83 years); most (66%) were younger than 45 years, and 14% were 60 years or older. Of the total number of patients enrolled, 58% were male and 84% were White. Notably, most patients had Stage IV disease (64%), 2 or 3 (53%) International Prognostic Factor Project (IPFP) risk factors, Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 (57%), extranodal involvement at diagnosis (62%), and B symptoms (59%) at baseline.

Efficacy Results

OS, PFS (per investigator), percentage of patients alive without HL, health-related quality of life measured with the European Organization for Research and Treatment of Cancer quality of life questionnaire core 30 (EORTC QLQ-C30), and European Quality of Life 5 Dimensions 3 Level Version (EQ-5D-3L) were obtained from the data with a cut-off date of June 1, 2021, while mPFS per independent review facility (IRF) was from the data with a cut-off date of April 20, 2017.

OS

As of the data cut-off date June 1, 2021, the median follow-up was 73.3 months (95% confidence interval [CI: 72.61 to 74.05) in the BV + AVD group and 72.4 months (95% CI: 71.10 to 73.63) in the ABVD group. In the intention-to-treat (ITT) population, the hazard ratio (HR) for OS was 0.59 (95% CI: 0.396 to 0.879; P = 0.009), favouring BV + AVD treatment. There was a 4% absolute difference in number of OS events between the BV + AVD (6%) and ABVD (10%) arms. Median OS was not reached for patients with advanced stage classical HL for either the BV + AVD group or the ABVD group. In subgroup analyses by disease stage, the HR for OS was 0.863 (95% CI: 0.452 to 1.648; P = 0.654) for patients with stage III classical HL and 0.478 (95% CI: 0.286 to 0.799; P = 0.004) patients with stage IV classical HL.

As of the data cut-off date of March 11, 2023, the descriptive analysis for OS had a median follow-up of approximately 88 months for the ITT population: The median follow-up duration (months) was 89.7 (95% CI: 86.57 to 90.55) for the BV + AVD group and 86.3 (95% CI: 84.53 to 89.33). This analysis included 111 OS events (deaths): 44 deaths (7%) were reported in the BV+ AVD group and 67 deaths (10%) in the ABVD group. Median OS was not reached for either group. The HR for OS was 0.61 (95% CI: 0.414 to 0.892, descriptive p=0.010). In the stage III subgroup, median OS was not reached for either treatment arm, and the HR for OS was 1.004 (95% CI: 0.540 to1.866) for BV+AVD patients, compared with ABVD patients. In the stage IV subgroup, median OS was not reached for either treatment arm, and the HR for OS was 0.48 (95% CI: 0.291 to 0.784; descriptive p=0.003) for BV+AVD patients, compared with ABVD patients.

Alive without HL, n (%)

In the ITT population, the 3-year rates of being alive without HL were 96% (546/567) in the BV + AVD group and 93% (503/540) in the ABVD group. The 5-year rates of being alive without HL were about 94% (450/480) in the BV + AVD group and 92% (408/443) in the ABVD group. No subgroup analyses by disease stage were reported for this efficacy endpoint.

PFS per investigator

As of the data cut-off date June 1, 2021, the median follow-up was 73.2 months (95% CI: 72.48 to 74.05) in the BV + AVD group and 71.6 months (95% CI: 70.37 to 72.87) in the ABVD group. In the ITT population, the HR of PFS per investigator was 0.678 (95% CI: 0.532 to 0.863; P = 0.002), favouring treatment with BV + AVD. There was a 7% absolute difference in number of PFS events between the BV + AVD group (17%) and the ABVD group (24%). Median PFS per investigator was not reached for patients with advanced stage classical HL for either the BV + AVD group or the ABVD group. In subgroup analyses by disease stage, the HR for PFS per investigator was 0.603 (95% CI: 0.391 to 0.930; P = 0.021) for patients with stage III classical HL and 0.715 (95% CI: 0.534 to 0.959; P = 0.024) patients with stage IV classical HL.

mPFS per IRF

As of the data cut-off date April 20, 2017, median mPFS was not reached in either the BV + AVD group or the ABVD group. In the ITT population, the HR for mPFS per IRF was 0.770 (95% CI: 0.603 to 0.982; P = 0.035). There was a 4% absolute difference in number of mPFS events between the BV + AVD arm and the ABVD arm, favouring BV + AVD (18% vs. 22%). In subgroup analyses by disease stage, the HR for mPFS per IRF was 0.923 (95% CI: 0.600 to 1.420; P = 0.716) for patients with stage III classical HL and 0.712 (95% CI: 0.530 to 0.957; P = 0.024) for patients with stage IV classical HL.

Harms Results

Deaths and secondary malignancies were from data cut-off date June 1, 2021, while the remaining data were from the data cut-off as of April 20, 2017.

In the safety population, the proportions of patients experiencing treatment-emergent adverse events (TEAEs) up to 30 days after last frontline dose were similar between patients treated with BV + AVD (99%) and patients treated with ABVD (98%). Higher percentages of patients in the BV + AVD group experienced treatment-emergent serious adverse events (TESAEs) up to 30 days after last frontline dose, compared to the percentages of patients in the ABVD group (43% vs. 27%). Deaths were reported in 6% of the patients in the BV + AVD arm and 10% of the patients in the ABVD arm. Treatment discontinuation due to adverse events (AEs) occurred in 13% of the patients in the BV + AVD arm and 16% of the patients in the ABVD arm. In terms of notable harms, 67% of the patients in the BV + AVD group and 43% in the ABVD group experienced at least 1 peripheral neuropathy event. About 3% of the patients in the BV + ABVD group and 5% of the patients in the ABVD group developed secondary malignancies. The proportion of patients who experienced neutropenia as TEAEs grade 3 or higher was higher in the BV + ABVD group than those in the ABVD group (54% vs. 39%). Similarly, the proportions of patients who experienced febrile neutropenia as TEAEs grade 3 or higher were also higher in the BV + ABVD group than those in the ABVD group (19% vs. 8%). Fewer patients in the BV + AVD arm experienced AEs of pulmonary-related toxicity than those in the ABVD arm (13% vs. 25%). The most common AE of pulmonary-related toxicity for either group was dyspnea (12% vs. 24%).

Critical Appraisal

Generally, no serious concerns were identified in the conduct of the ECHELON-1 trial. However, the validity of the primary outcome (mPFS) is a key consideration in evaluating the evidence for BV + AVD. mPFS was adopted in the ECHELON-1 trial with the aim to capture all events that reflect a failure of frontline chemotherapy by counting a response that was less than complete at the end of the frontline therapy as an event. The ECHELON-1 trial defined the response less than complete as "*receipt of anticancer therapy or radiotherapy for HL after completion of frontline therapy for patients who were confirmed non-complete responders*." However, the clinical experts consulted by the review team noted that this definition is not consistent with practice in defining disease progression or first-line treatment failure in advanced HL, and receipt of radiotherapy does not necessarily indicate disease progression in clinical practice. Despite the end-of-treatment PET scans conducted by IRF, there is a concern that the results for mPFS would be biased given the administration of new anticancer therapy was at the discretion of the treating physician. The clinical experts consulted by the review team noted that OS and PFS are more clinically relevant to assessing patients' benefit from treatment, and no evidence was included in the submission to the review team empirically validating mPFS as an outcome measure or that established a correlation with OS. High percentages in loss to follow-up and withdrawal by patients were noted in both OS and PFS analyses. Although the percentages of loss to follow-up and withdrawal by patients were balanced between treatment arms, reasons for loss-to-follow up and withdrawal could be differential between groups, which consequently might lead to biased estimates of treatment

effects. Moreover, sensitivity analyses assessing the potential impact of the loss to follow-up and withdrawal on OS and PFS results were not available. Subgroup analyses by HL stage signal that there might be a difference in treatment effects between patients with stage III and those with stage IV classical HL for mPFS and OS. However, the review team's ability to make definitive conclusion on whether the difference between the disease stage subgroups is true was limited by several concerns, such as the balance of known and unknown factors between treatment groups achieved by randomization may not have been preserved in stage III or stage IV subgroups as well as the trial was not specifically designed to test statistical inferences between BV + AVD and ABVD in stage III and stage IV subgroups.

All participants in the ECHELON-1 trial were required to be ≥ 18 years of age and diagnosed with classical HL. Therefore, the ECHELON-1 trial did not reflect results for pediatric patients or patients with nodular lymphocyte-predominant HL. The eligibility criteria of the ECHELON-1 trial in general were aligned with selection criteria in the Canadian settings when identifying suitable candidates for BV + AVD, according to the clinical experts consulted by the review team. However, the clinical experts noted that in clinical practice, a small percentage of patients who were excluded from the ECHELON-1 trial might be eligible to receive BV + AVD, such as patients with HIV as long as the disease is well managed and to patients with borderline LVEF after consultation with cardiologist. The clinical experts also noted that patients with higher ECOG PS scores (> 2) could be considered for treatment with BV + AVD on a case-by-case basis. The clinical experts noted that the doses of BV + AVD and ABVD used in the ECHELON-1 trial generally reflected the standard dose schedules used for adults in Canada. The clinical experts also confirmed that the direct comparator, ABVD up to 6 cycles (not adapted based on PET response), is a relevant therapy used in current standard of care, although it is not the only standard of care frontline therapy used in Canada and therefore there are other relevant comparators. In addition, the clinical experts noted that the percentages of patients who received transplant as subsequent treatment were lower in either group than they would have expect in clinical practice. According to the clinical experts consulted by the review team, the study population characteristics generally reflected patients who would be eligible for BV + AVD in Canadian practice. However, the clinical experts noted that the percentage of patients with stage IV HL in the trial population and the percentage of White participants were higher than one would see in clinical practice.

Long-Term Extension Studies

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

Indirect Comparisons

No indirect treatment comparisons (ITCs) were submitted by the manufacturer. The manufacturer provided a feasibility assessment that determined it would be infeasible to conduct ITCs of BV + AVD versus other frontline therapies examined in clinical studies for advanced HL.

Studies Addressing Gaps in the Pivotal and RCT Evidence

To address gaps in the pivotal RCT evidence related to the use of BV in pediatric patients with advanced HL, the review team reviewed evidence from an additional phase III RCT.

Description of studies

The AHOD1331 trial (N = 587)[12], published in *The New England Journal of Medicine*, is a phase III, multi-center, open-label, randomized active-controlled trial comparing BV in combination with doxorubicin, vincristine , etoposide, prednisone, cyclophosphamide (BV + AVEPC) with doxorubicin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide (ABVE-PC) in previously untreated patients aged ≥ 2 years and < 22 years with high-risk classical HL, defined as Ann Arbor stage IIB with bulk tumour, stage IIIB, stage IVA and stage IVB patients. The primary objective of the AHOD1331 trial was to determine the efficacy of BV + AVEPC relative to ABVE-PC measured by event-free survival (EFS). OS and harms outcomes were also reported. The AHOD1331 trial is ongoing. The final analysis of EFS was based on the database lock date of December 31, 2021.

In the AHOD1331 trial, the median age of participants was 15.6 years (range: 3.4 to 21.99 years); most (84.7%, 497/587) were between 12 and 22 years. Of the total number of patients enrolled, 47% (276/587) were female and 57.6% (338/587) were Non-Hispanic White. The proportions of patients by disease stage were 20.6% (121/587) for stage IIB with bulk tumour, 19.3% (113/587)

for stage IIIB, 28.4% (167/587) for stage IVA, and 31.7% (186/587) for stage IVB. Most of the patients had nodular sclerosis classical HL (76.5%, 449/587).

Efficacy Results

The median follow-up time was 42.1 months (range: 0.1 to 80.9). In terms of the 3-year OS in the ITT population, the proportion of patients who were censored was 99.3% (95% CI: 97.3 to 99.8) in the BV + AVEPC group and 98.5% (95% CI: 96.0 to 99.4) in the ABVE-PC group, respectively. The HR for 3-year OS was not provided.

In terms of the 3-year EFS in the ITT population, the proportion of patients who were censored was 92.1% (95% CI: 88.4 to 94.7) in the BV + AVEPC group and 82.5% (95% CI: 77.4 to 86.5) in the ABVE-PC group, respectively. The HR for 3-year EFS was 0.41 (95% CI: 0.25 to 0.67, P < 0.001) favouring the BV + AVEPC arm.

Harms Results

The incidence of any AEs of grade 3 or higher was 73.5% in patients treated with BV + AVEPC and 68.2% in patients treated with ABVE-PC. Peripheral neuropathy of grade 3 or higher occurred in 6.7% of the patients in the BV + AVEPC arm and 5.5% % of the patients in the ABVE-PC arm. Febrile neutropenia occurred in 30.9% and 32.5% of patients in the BV + AVEPC arm and patients in the ABVE-PC arm, respectively. None of the patients in the BV + AVEPC group experienced pneumonitis compared to 1 patient in the ABVE-PC group.

Critical Appraisal

Although details about the randomization process and allocation concealment were not reported in the research protocol or the main article, the risk of bias in the AHOD1331 trial is anticipated to be low given that baseline characteristics between the treatment arms were generally similar for clinically important factors. The AHOD1331 trial was open-label but had blinded outcome assessors, the definition of EFS was aligned with accepted definitions from regulators, and treatment response was assessed via centralized review, thus helping to reduce the risk of detection bias related to the open-label design. Despite that patients were aware of the treatment allocation which might result in performance bias, this risk is considered low due to reasons such as the 3-year PFS in the ABVE-PC group (82.5%) and the types of AEs were generally in line with what is expected by the clinical expert who specializes in pediatric oncology consulted by the review team. Those patients who remained PET positive after 2 cycles of chemotherapy received response-adapted involved site radiation therapy guided by blinded central assessment of PET scans. This could bias EFS results if the radiation therapy could improve response, reduce the likelihood of relapse, and/or increase the risk of secondary malignancy. However, the risk of this potential bias was mitigated by the requirement that radiation therapy could not be administered until directed to do so from the blinded assessment. Also, the percentages of patients who received involved-site radiation therapy were similar between the BV + AVEPC group and the ABVE-PC group (53.4% vs. 56.8%). Concomitant anticancer medications were not allowed. Antibiotics and supportive medications (e.g., antiemetics) were permitted as needed. As well, patients received G-CSF support. None of the permitted medications would likely influence the results for either treatment group. However, after a progression event, the treating physician could treat the patient at their discretion, which may impact the longer-term OS results.

The AHOD1331 trial was appraised in this section to address an important gap with respect to the unmet needs of using BV + chemotherapy in pediatric patients with classical HL. However, there are several notable issues which need to be considered when generalizing results from the AHOD1331 trial. First, the chemotherapy backbone used in the AHOD1331 trial (i.e., AVEPC), although a preferred backbone for pediatric patients according to POGO and the clinical expert consulted by the review team, is different from the backbone used in adults (i.e., ABVD). Regarding the regulatory status of the pediatric regimen, the review team confirmed that BV is not approved for use in combination with the pediatric regimen and the manufacturer has confirmed they are not planning to file for Health Canada approval for BV + AVEPC. Second, the clinical experts consulted by the review team noted the definition of high-risk/advanced stage HL in pediatric patients is varying. While the AHOD1331 trial adopted the definition of advanced stage HL in pediatric patients as stage II with bulk tumour, stage IIIB, stage IVA, and stage IVB, some medical centers may define any stage III or IV as advanced stage disease in pediatric patients. Finally, the AHOD1331 trial involved both non-adults and young adults (up to 22 years old), while the pivotal ECHELON-1 trial enrolled patients 18 years and older. Therefore, there was an overlap in patient age between the pivotal ECHELON-1 trial and the AHOD1331 trial. The clinical expert consulted by the review team noted that the chemotherapy backbone AVEPC used in the AHOD1331 trial would not typically be used in patients aged ≥ 18 years in Canada, and

the chemotherapy backbone ABVD investigated in the pivotal ECHELON-1 trial may be used in adolescents aged close to 18 years with HL.

Economic Evidence

Cost and Cost-Effectiveness

Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Semi-Markov model
Target population	Previously untreated patients with advanced stage HL
Treatment	Brentuximab vedotin in combination with doxorubicin, vinblastine, and dacarbazine (BV+AVD)
Dose regimen	1.2 mg/kg of body weight, given intravenously, on days 1 and 15 of each 28-day cycle for up to six cycles
Submitted price	$4,840.00 per 50 mg vial
Treatment cost	BV+AVD regimen = $21,584 over a 28-day cycle
Comparator	Doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD)
Perspective	Canadian publicly funded health care payer
Outcome	QALYs, LYs
Time horizon	Lifetime (60 years)
Key data source	ECHELON-1 trial, an open-label, multicenter, randomized phase 3 trial
Key limitations	• Transitions probabilities from the frontline progression free health state were based on investigator assessed PFS. Given the open-label nature of ECHELON-1, PFS by investigators might be prone to detection bias. Therefore, there is uncertainty in PFS estimates, which drive the benefits associated with BV+AVD. • The manufacturer model did not assess the cost-effectiveness of BV in pediatrics. Given all participants of the pivotal trial used to populate the economic model (ECHELON-1) were required to be ≥ 18 years of age, the ECHELON-1 trial and manufacturer's economic evaluation did not reflect pediatric patients. Therefore, the clinical efficacy and cost-effectiveness of BV+AVD in the pediatric population is unknown. To address the significant unmet needs in the pediatric patient population, the AHOD1331 trial, which used a different chemotherapy backbone (AVEPC) than the ECHELON-1 trial, was examined by the CADTH clinical review report. CADTH was unable to incorporate data from the AHOD1331 trial into the manufacturer's model. As such, the cost-effectiveness of BV + AVEPC is unknown. • BEACOPP,PET- adapted ABVD and PET- adapted BEACOPP are relevant comparators and were not included in the economic evaluation. The cost-effectiveness of BV+AVD compared with BEACOPP or PET-adaptation of ABVD or BEACOPP is unknown. • The manufacturer's Markov model structure was limited for several reasons. First, patients with different stages of advanced HL (stage III or IV) are heterogenous as they have distinct prognoses. Likewise, the effect of treatment on PFS, and OS may vary depending on stage, according to the clinical review report. As analyses stratified by subgroup were not incorporated in the model, the review team could not assess the cost-effectiveness of BV+AVD by disease stage. Second, in the post progression and receipt of an ASCT health state, the manufacturer did not differentiate between patients who were cured by ASCT and those who were not. This meant that in this health state, both cured and not cured patients had the same utility values and survival, which lacks face validity. • The manufacturer adopted treatment-specific health utility values instead of health state-specific utilities as recommended by CADTH guidelines. In addition, the manufacturer did not include AE disutilities in the base case. • The proportion of patients undergoing ASCT upon frontline failure obtained from the ECHELON-1 trial was considered underestimated and not reflective of Canadian clinical practice.

Component	Description
	• In the progression free health state, the manufacturer did not include any monitoring costs such as physicians' visits or assessments. This approach lacked face validity and favoured BV+AVD. • The manufacturer applied RDI in the derivation of some drug costs. This is inappropriate as RDI can be influenced by many different factors that do not perfectly correlate with cost.
CADTH reanalysis results	• CADTH undertook reanalyses to address several key limitations, by using health state-specific utilities, including disutilities for AEs, and eliminating RDI. • In the CADTH base case, BV+AVD was associated with an ICER of $115,865 per QALY gained compared to ABVD (inc. costs = $105,110; inc. QALYs = 0.91). Note that as the manufacturer's model used ECHELON-1 trial data which excluded pediatric patients, results represent cost-effectiveness of BV+AVD for the treatment of previously untreated adult patients with advanced stage HL. • A price reduction of at least 55% (from $4,840 to $2,178 per 50 mg vial) is required for BV+AVD to be cost-effective at a WTP threshold of $50,000 per QALY gained compared ABVD.

Budget Impact

- CADTH identified the following key limitations with the manufacturer's analysis: relevant comparators were excluded, public coverage was inappropriate, and the market uptake for BV+AVD in the stage III and IV HL was underestimated.
- CADTH base-case case revisions included: increasing the public coverage rate, increasing the market uptake for patients with stage III and IV HL, and increasing the number of vials per cycle for specific drug therapies. CADTH reanalyses suggest the budget impact for funding BV+AVD for advanced stage HL (in both the adult and pediatric population) is expected to be $35,066,197 over three years (Year 1: $10,658,052; Year 2: $11,681,771; Year 3: $12,726,344). Note that in CADTH's base case, pediatric patients were included and it was assumed that the chemotherapy backbone and comparator treatment they will receive is identical to adults, which is contradictory to feedback provided by clinical experts for this review.
- In a scenario that CADTH conducted in an adult only population, CADTH estimated that there are approximately 13 pediatric patients per year in the pan Canadian BIA (39 pediatric patients over 3 years). Based on the cost-comparison table, the 28-day cycle costs of treating pediatric patients with BV + AVEPC is $21,110, or $105,551 for 5 cycles of treatment. As such, the cost of treating pediatric HL patients with BV + AVEPC would be approximately $1,372,165 per year (assuming 13 patients are treated per year).

pERC Information

Members of the Committee:

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Philip Blanchette, Dr. Kelvin Chan, Dr. Matthew Cheung; Dr. Michael Crump, Dr. Jennifer Fishman, Mr. Terry Hawrysh, Dr. Yoo-Joung Ko, Dr. Christian Kollmannsberger, Dr. Catherine Moltzan, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

Meeting date: July 10, 2024

Regrets:

Two expert committee members did not attend.

Conflicts of interest:

Two expert committee members did not participate due to considerations of conflict of interest.