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CADTH PCODR INITIAL CLINICAL GUIDANCE REPORT

# Clinical Report

## BRENTUXIMAB VEDOTIN (ADCETRIS)

**(Seattle Genetics, Inc.)**

**Indication:** for the treatment of previously untreated patients with Stage IV Hodgkin lymphoma (HL) in combination with doxorubicin, vinblastine, and dacarbazine (AVD).


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# Abbreviations

| | |
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| **ABVD** | doxorubicin, bleomycin, vinblastine, dacarbazine |
| **AE** | adverse event |
| **ALT** | alanine aminotransferase |
| **AST** | aspartate aminotransferase |
| **ATA** | antitherapeutic antibodies |
| **ANC** | absolute neutrophil count |
| **ASCT** | autologous stem cell transplantation |
| **BEACOPP** | bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone |
| **BrECADD** | etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone |
| **BSA** | body surface area |
| **BV** | brentuximab vedotin |
| **BV + AVD** | brentuximab vedotin in combination with doxorubicin, vinblastine, dacarbazine |
| **CAPDac** | cyclophosphamide, brentuximab, prednisone, dacarbazine |
| **CGP** | clinical guidance panel |
| **CHF** | congestive heart failure |
| **cHL** | classic Hodgkin lymphoma |
| **CI** | confidence interval |
| **CR** | complete remission |
| **CrCl** | creatinine clearance |
| **CT** | computerized tomography |
| **DFS** | disease-free survival |
| **DOR** | duration of response |
| **DOCR** | duration of complete remission |
| **DS** | Deauville Score |
| **ECADD** | etoposide, cyclophosphamide, doxorubicin, dacarbazine |
| **ECG** | electrocardiogram |
| **ECOG PS** | Eastern Cooperative Oncology Group Performance Status |
| **EFS** | event-free survival |
| **EMA** | European Medicines Agency |
| **EORTC** | European Organization for Research and Treatment of Cancer |
| **EOT** | end of treatment |
| **EPAR** | European public assessment report |
| **EQ-5D-3L** | EuroQoL 5-Dimension (3-level version) |
| **FACT/GOG-Ntx** | Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity |
| **FACIT-Dyspnea** | Functional Assessment of Chronic Illness Therapy – Dyspnea |
| **FDG-PET** | fluorodeoxyglucose-positron emission tomography |
| **G-CSF** | granulocyte colony-stimulating factor |
| **HBV** | hepatitis B virus |
| **HC** | Health Canada |
| **HCV** | hepatitis C virus |
| **Hg** | hemoglobin |
| **HIV** | human immunodeficiency virus |
| **HL** | Hodgkin lymphoma |
| **HR** | hazard ratio |
| **HRQoL** | health-related quality of life |
| **IFPF** | International Prognostic Factor Project |
| **IRF** | independent review facility |
| **IPS** | International Prognostic Score |
| **ITT** | intention-to-treat |
| **IV** | intravenous |
| **IWG** | International Working Group |
| **K-M** | Kaplan-Meier |
| **LTFU** | long-term follow-up |
| **LVEF** | left ventricular ejection fraction |
| **MedDRA** | Medical Dictionary for Regulatory Activities |

| | |
|---|---|
| **MI** | myocardial infarction |
| **NCI CTCAE** | National Cancer Institute Common Terminology Criteria for Adverse Events |
| **mPFS** | modified progression-free survival |
| **NYHA** | New York Heart Association |
| **ORR** | objective response rate |
| **OS** | overall survival |
| **PAG** | provincial advisory group |
| **pERC** | pCODR Expert Review Committee |
| **PET** | positron emission tomography |
| **PET2** | treatment cycle 2 PET |
| **PK** | pharmacokinetic |
| **PLT** | platelet |
| **PML** | progressive multifocal leukoencephalopathy |
| **PP** | per protocol |
| **PRO** | patient-reported outcome |
| **QoL** | quality of life |
| **QLQ-C30** | Quality of Life Questionnaire Core 30 |
| **RR** | relative risk |
| **RT** | radiotherapy |
| **SAE** | serious adverse event |
| **SCr** | serum creatinine |
| **SMQ** | Standardised MedDRA Query |
| **TEAE** | treatment-emergent adverse events |
| **WDAE** | withdrawal due to adverse event |

# 1 Guidance In Brief

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies brentuximab vedotin (Adcetris) for Hodgkin Lymphoma (HL). The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on: a systematic review of the literature conducted by the Clinical Guidance Panel (CGP) and the CADTH Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; input from Registered Clinicians; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input, a summary of submitted Provincial Advisory Group Input, and a summary of submitted Registered Clinician Input, are provided in Sections 2, 3, 4, and 5 respectively.

## 1.1 Introduction

The objective of this review is to evaluate the efficacy and safety of brentuximab vedotin (Adcetris), in combination with doxorubicin, vinblastine, and dacarbazine (AVD), compared to standard of care in Canada for previously untreated patients with Stage IV Hodgkin lymphoma (HL).

Health Canada has issued a marketing authorization, without conditions, for brentuximab vedotin for the treatment of previously untreated patients with Stage IV HL in combination with AVD. The Health Canada indication aligns with the CADTH requested reimbursement criteria.

Brentuximab vedotin is an antibody-drug conjugate, which selectively targets tumor cells expressing the CD30 antigen. The Health Canada recommended dose is 1.2 mg/kg up to a maximum of 120 mg in combination with AVD administered every 2 weeks for a maximum of 12 doses or until disease progression or unacceptable toxicity. Brentuximab vedotin is administered as an intravenous infusion over 30 minutes. Primary prophylaxis with G-CSF is recommended beginning in Cycle 1 for patients who receive treatment with ADCETRIS + AVD for previously untreated Stage IV HL.[1]

## 1.2 Key Results and Interpretation

### 1.2.1 Systematic Review Evidence

One randomized controlled trial was identified that met the selection criteria of this review. ECHELON-1 was an ongoing, international, multi-centre, open-label, Phase III, randomized superiority trial that compared brentuximab vedotin (BV) in combination with doxorubicin, vinblastine, dacarbazine (BV + AVD) to the combination regimen of doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD) in patients with previously untreated advanced classic Hodgkin lymphoma (cHL). Patients ≥ 18 years of age with Stages III or IV cHL were randomized in a 1:1 ratio to receive up to six cycles of either BV + AVD or ABVD, with the combinations administered on Day 1 and 15 of each 28-day cycle for a maximum of 6 cycles. The study enrolled 1,334 patients, with 664 randomized to the BV + AVD and 670 patients randomized to the ABVD treatment groups; randomization was stratified according to region (Americas vs. Europe vs. Asia) and number of International Prognostic Factor Project (IPFP) risk factors (International Prognostic Score [IPS] 0-1 vs. 2-3 vs. 4-7).[2] Sixty patients treated in Canada were enrolled in this trial.[3]

During the treatment phase, tumour measurements via positron emission tomography (PET) and computerized tomography (CT) scans were performed at baseline, after Cycle 2, and at the end of treatment (EOT). CT scan results were used to help assess treatment response and disease status, according to the Revised Response Criteria for Malignant Lymphomas, and assessed by investigators as well as by an independent review facility (IRF). PET scans were also assessed by the blinded IRF using the Deauville criteria. During treatment, if PET scan results from Cycle 2 showed a Deauville score of 5, physicians had the option of switching the patient's treatment to an alternative regimen. Upon completion of frontline treatment, noncomplete response was defined as Deauville Score of 3-5 on the EOT PET scan.[2] Thereafter, patients were enrolled in the follow-up phase which was

originally planned for 5-years after randomization, though this was extended to 10 years in a protocol amendment made after primary study publication.[2,3]

The primary outcome was modified progression-free survival (mPFS), defined as time from date of randomization to the date that the first of the following occurred: 1) documented progressive disease; 2) death due to any cause; or 3) 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. Overall survival was the key secondary outcome. Several other secondary outcomes, including complete remission rate, were also investigated. Patient-reported outcomes (PROs) during treatment and follow-up, measured using EORTC QLQ-C30, were considered secondary endpoints. Other assessments such as FACIT-Dyspnea 10, FACT/GOG-Ntx, and EuroQoL 5-Dimension (EQ-5D-3L) were considered as part of exploratory analyses. Analysis of mPFS was also performed for several pre-specified subgroups, including age (< or ≥ 60 years), region (North America, Europe, Asia), Eastern Cooperative Oncology Group Performance Status (ECOG PS; 0,1,2), number of IPFP risk factors (0-1, 2-3, 4-7), and baseline cancer stage (Stage III, IV).[2]

Patient enrollment occurred over approximately three years. The median duration of follow-up was 24.6 months, with data cut-off date of April 20, 2017 for final mPFS analysis and interim OS analysis. At the time of the data cut-off date, 91 patients (14%) in the BV + AVD group and 123 patients (18%) in the ABVD group had discontinued from the study.[2,4] The final analysis of OS data is planned for when 112 deaths have occurred.[2]

Baseline demographics and characteristics were generally well balanced between the two treatment groups. Overall, the median age of enrolled patients was 36 years; slightly more males than females were enrolled. Notably, more patients had Stage IV disease (64%, n=846), IPFP risk factors 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.[2] Specific to the funding request of patients with Stage IV disease, which includes 425 patients in the BV + AVD treatment group and 421 patients in the ABVD group, the demographics and baseline characteristics were generally similar to the overall population and well balanced between both groups. However, compared to the overall population, patients with Stage IV disease had higher IPFP risk factors (score 4-7; 26% in overall population vs. 35% Stage IV) and had more bone marrow (22% overall population vs. 33% Stage IV) as well as extranodal involvement (62% overall population vs. 85% Stage IV).[4]

Most patients (89% of BV + AVD vs. 91% of ABVD) completed six cycles of randomized treatment. During frontline treatment, 15 patients (2%) in the BV + AVD group and 9 patients (1%) in the ABVD group switched to alternative chemotherapy, mainly due to having a Deauville score of 5 or an adverse event. After completing frontline therapy, 18% of patients treated with BV + AVD (n=121) received at least one subsequent anticancer therapy compared to 22% of patients treated with ABVD (n=144). The most commonly used anticancer therapy was combination chemotherapy.[4] Due to the higher incidence of neutropenia in the BV + AVD group, the independent data and safety monitoring committee recommended primary prophylaxis with G-CSF; this change was made after 75% of enrolment was complete. Based on the definition of primary prophylaxis, which was administration before Day 5, 83 patients (13%) in the BV + AVD group and 43 patients (7%) in the ABVD group received G-CSF.[2]

All efficacy analyses were performed in the intention-to-treat (ITT) population, and the safety analysis included patients who received at least one dose of study medication.[2]

*Efficacy*

A brief summary, highlighting the key outcomes of the trial, is provided in Table 1. As of the data cut-off date, median mPFS had not been reached in either treatment group.[2] Overall, 263 mPFS events had been observed: 117 (17.6%) in the BV + AVD group and 146 (21.8%) in the ABVD group, mostly due to disease progression.[4] A small proportion of patients (n=9, 1% of BV + AVD; n=22, 3% of ABVD group) experienced modified progression, most of whom received salvage chemotherapy as subsequent treatment; 2 patients treated with BV + AVD and 7 patients with ABVD received radiotherapy. The 2-year mPFS rate was higher in patients treated with BV + AVD compared to ABVD (82.1% vs. 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 + AVD treatment. Most results of the pre-specified exploratory mPFS subgroup analyses were consistent with the results of mPFS in the ITT population with some subgroups of patients appearing to derive more benefit with BV + AVD compare with ABVD than others, including patients with Stage IV disease with unstratified HR of 0.71 (95% CI, 0.53 to 0.96)[4]. However, it is important to note that 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.[2] An updated post-hoc exploratory analysis of investigator-assessed progression-free survival 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.[5,6]

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 + AVD and 39 deaths in ABVD groups, with estimated 2-year interim overall survival rates of 96.6% and 94.2% for patients treated with BV + AVD and ABVD, respectively.[2] Final OS analysis was still not performed at the time of the four-year follow-up.

Complete remission according to IRF, a secondary endpoint, was achieved by a high proportion of patients at the end of randomized treatment: 488 patients (73%) in the BV + AVD group and 472 patients (70%) in the ABVD group, with corresponding relative risk of 1.04 (95% CI, 0.97 to 1.11).[4] A higher proportion of patients with Stage III disease had achieved CR (80% in BV + AVD; 74% in ABVD) compared to those with Stage IV disease (70% in BV + AVD vs. 69% in ABVD).[4] Of patients who achieved CR, 22 (3%) in the BV + AVD group and 24 (4%) in the ABVD group subsequently received at least one anticancer therapy as a result of disease progression during follow-up. Most patients who had progressed after achieving CR were started on chemotherapy, with brentuximab-based regimens prescribed to ten patients in the ABVD group.[7]

For the EORTC QLQ-C30 subscale scores of global health status/QoL showing change from baseline to EOT, there was generally a decrease in scores in the BV + 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.[8] Similarly, mean summary scores over time across treatment cycles were lower in the BV + AVD group; however, during post-treatment follow-up, scores had returned to baseline levels or better.[4] A similar pattern was seen for the exploratory PRO measures. During treatment, a trend of worsening dyspnea and functional limitation was observed in both groups using FACIT-Dyspnea 10. Scores were generally higher (indicating worse symptoms and functional limitation) in patients treated with BV + AVD but the difference between the two groups were not clinically meaningful.[4] 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 + AVD.[3] There was no difference seen in the EQ-5D-3L mean scores between the two treatment groups.[4] Although overall PRO results may be of potential concern, suggesting that BV + AVD may lead to experiencing a lower quality of life and function, such impact seem to be limited to the treatment period, without long-term effects.

*Safety*

Compared to the ABVD treatment group, more patients receiving BV + AVD experienced severe treatment-emergent adverse events (TEAEs) of Grade ≥ 3, serious TEAEs, and drug-related AEs. Hospitalizations, mainly due to adverse events, occurred in more patients treated with BV + AVD (37% vs. 28% for ABVD). A higher rate of pulmonary-related toxicity of any grade was seen in patients treated with ABVD (7%) compared to BV + AVD (2%). Most notably, the following TEAEs of any grade (occurring in at least 10% of the patients in either group) were reported in a greater proportion of patients treated with BV + AVD compared to ABVD: neutropenia (58% vs. 45%), febrile neutropenia (19% vs. 8%), and any peripheral neuropathy (Standardised MedDRA Query [SMQ]) event (67% vs. 43%). Implementation of G-CSF prophylaxis in patients receiving BV + AVD resulted in relatively lower rates of neutropenia and infection compared to those who had not received primary prophylaxis, though rates remained higher than in patients in the ABVD group who received G-CSF prophylaxis. At the time of the last follow-up visit, 43% of patients treated with BV + AVD who had developed peripheral neuropathy experienced resolution and 24% of patients experienced an improvement by at least one grade; residual symptoms were mostly Grade 1 or 2 in severity.[2] Three and four-year follow-up data showed continued improvement or resolution in peripheral neuropathy in both treatment groups. At four-years, complete resolution of peripheral neuropathy in the BV + AVD group had occurred in most affected patients (68%) and was documented at median of 30 weeks.[5]

In patients treated with BV + AVD, the most commonly reported drug-related serious adverse event (SAEs), reported for at least 5 patients, included febrile neutropenia (17%), pyrexia (6%), neutropenia (3%), pneumonia (2%), abdominal pain (2%), and sepsis (2%). In patients who received ABVD, the most frequently reported drug-related SAEs included febrile neutropenia (6%), pyrexia (3%), and pneumonitis (2%).[4] Discontinuation of one or more of the treatment combination components due to an AE was higher in

the ABVD group (16%) than the BV + AVD group (13%).[2] The most frequently reported TEAEs leading to premature drug discontinuation (reported for at least two patients) in the BV + AVD group were peripheral sensory neuropathy, peripheral neuropathy, peripheral motor neuropathy, and febrile neutropenia. For patients treated with ABVD, the most frequently reported TEAE resulting in premature study drug discontinuation were dyspnea, pulmonary toxicity, cough, reduced carbon monoxide diffusing capacity, and pneumonitis. Most interventions for BV involved dosage reduction, delay, or discontinuation; the BV component of the combination was discontinued permanently in 71 patients (11%). Discontinuation of the entire treatment combination due to an adverse event occurred in 4% of patients treated with BV + AVD and 3% of patients who received ABVD.[4]

A similar pattern of drug-related AEs was seen in patients with Stage III and IV disease compared to the overall population. However, specific to the BV + AVD treatment group, patients with Stage III disease had higher incidence of the following compared to those with baseline Stage IV cHL: serious TEAE (48% vs. 40%), drug-related SAE (42% vs. 33%), and AE resulting in study drug discontinuation (19% vs. 10%).[4]

During the treatment phase, 9 deaths were recorded in the BV + AVD group compared to 13 deaths in the ABVD group. In patients treated with BV + AVD, 8 of the 9 deaths were deemed to be due to a drug-related AE, of which 7 were associated with neutropenia and its complications; of note, the deaths occurred in patients who had not received G-CSF primary prophylaxis. In patients who received ABVD, 7 out of the 13 on-study deaths were deemed to be drug-related, with the majority being due to pulmonary-related toxicity.[4]

*Limitations*

Overall, the ECHELON-1 trial was a well-designed RCT and there were no major concerns with the conduct of the trial. The randomization method and sample size were adequate, and a stratified randomization procedure was used based on known prognostic factors to minimize potential imbalances between the study groups that might lead to biased results. Eligibility criteria were well defined and appropriate; the study population characteristics reflect patients who would be eligible for BV + AVD in Canadian practice, and baseline characteristics between groups were generally well balanced. The populations used for analyses were appropriate, with the key efficacy analysis conducted according to the ITT principle. The study protocol was approved by institutional review boards and ethics committees at each study center and the trial was conducted in accordance with Good Clinical Practice guidelines. However, there are a few key limitations and potential sources of bias that were noted by the CADTH Methods Team:

- The population of the ECHELON-1 trial is broader than the reimbursement request in this CADTH submission. Patients with Stage III and IV were eligible for inclusion into the trial. However, this reimbursement request is limited to patients with Stage IV disease only. Therefore, the request is for a subpopulation of the trial and not for the ITT population. 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 Health Canada (HC) approved indication was limited to patients with Stage IV, although the Sponsor's request to HC included the full trial population. It appears that a precautionary approach was taken by HC due to uncertainties regarding efficacy (including inconsistency in observed mPFS benefit between Stage III and IV subgroups, immature OS data, and use of surrogate endpoint); 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 patients. HC provided an approved indication for Stage IV disease, based on an overall positive study with inconsistent results from key subgroups but a trend for positive mPFS for Stage IV patients.
  The updated efficacy analysis performed after 3- and 4-years patient follow-up reported traditional PFS, which was an exploratory analysis. This longer follow-up data had not been included in the HC assessments. These updated results should be interpreted with caution as the trial was not originally designed to measure PFS, and this endpoint was measured by investigators, which is subject to bias. The latest available data for the post-hoc PFS analyses showed that the magnitude of benefit with both Stage III and IV disease were consistent with the ITT population and favoured BV + AVD, which appears to be reflective of benefit seen over a longer time frame.

- 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 were blinded to treatment.
- The primary endpoint 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. Current OS data is still immature and reflects interim analysis. Nonetheless, according to the CGP, measured outcomes were clinically important and relevant to patients with cHL.
- During the study follow-up period, patients were permitted to receive subsequent treatment for HL, which included brentuximab vedotin (39 patients [6%] in ABVD group). Overall, 18% of patients in the BV + AVD group and 22% in the ABVD group received at least one subsequent anticancer therapy.[4] This may confound the assessment of OS by prolonging survival beyond what would have occurred with frontline treatment alone, but this reflects clinical practice.
- Subgroup and sensitivity analyses were prespecified, though were considered exploratory and not adjusted for multiplicity. The primary endpoint was supported by several consistent sensitivity analyses; however, results from subgroup analyses were inconsistent. While most point estimates of hazard ratios for the subgroups suggested benefit with BV + AVD, and were consistent with the ITT population, some subgroups of patients (e.g., male, age < 65 years, Stage IV disease, from North America or Americas) appeared to derive more benefit with BV + AVD compared with ABVD than others. Confidence intervals of other subgroups crossed 1.0, and the subgroup of older patients did not show a treatment benefit (e.g., ≥65 years; HR 1.01; 95% CI 0.53 to 1.94). However, small sample sizes, wide confidence intervals, and high rate of censoring contribute to the uncertainty and caution is required in interpretation of these data.[4]
- Patient-reported outcomes were not included in the adjustment for multiplicity. Overall, interpretation of QoL end points is limited.

## Table 1: Highlights of Key Outcomes

| | ECHELON-1 | |
|---|---|---|
| | **BV + AVD** | **ABVD** |
| **Efficacy – Overall ITT Population** | **N=664** | **N=670** |
| **Primary Outcome – mPFS by IRF** | | |
| Median, months (95% CI) | NE (48.2 to NE) | NE (NE to NE) |
| Events, n (%) | 117 (17.6) | 146 (21.8) |
| HR (95% CI)* | 0.77 (0.60 to 0.98) | |
| p-value | p=0.04 | |
| **Secondary Outcome (Key) – OS** | | |
| Median, months (95% CI) | NE (NE to NE) | NE (NE to NE) |
| Deaths, n (%) | 28 (4.2) | 39 (5.8) |
| HR (95% CI)* | 0.73 (0.45 to 1.18) | |
| p-value | p=0.20 | |
| **Secondary Outcome – CR at end of randomized treatment** | | |
| Rate, n (%) | 488 (73.5) | 472 (70.4) |
| RR (95% CI) | 1.04 (0.97 to 1.11) | |
| **Efficacy – Key Subgroup, Ann Arbor Stage at Diagnosis** | | |
| **Stage III, mPFS by IRF** | N=237 | N=246 |
| Events, n (%) | 40 (16.9) | 43 (17.5) |
| Unstratified HR (95% CI)* | 0.92 (0.60 to 1.42) | |
| **Stage IV, mPFS by IRF** | N=425 | N=421 |
| Events, n (%) | 77 (18.1) | 102 (24.2) |
| Unstratified HR (95% CI)* | 0.71 (0.53 to 0.96) | |
| **HRQoL – EORTC QLQ-C30 Global Health Status/QoL Subscale** | | |
| **Baseline** | N=648 | N=651 |
| LS Mean (SE) | 63.839 (0.9983) | 62.363 (0.9938) |
| LS Mean Difference (95% CI) | 1.476 (-0.901 to 3.852) | |
| **Difference from baseline to Cycle 2**† | N=609 | N=609 |
| LS Mean (SE) | -1.989 (0.8571) | 3.104 (0.7728) |
| LS Mean Difference (95% CI) | -5.094 (-7.130 to -3.057) | |
| **Difference from baseline to Cycle 6**† | N=537 | N=570 |
| LS Mean (SE) | -3.374 (0.8552) | 1.127 (0.8043) |
| LS Mean Difference (95% CI) | -4.501 (-6.582 to -2.420) | |
| **Harms Outcome, n (%)** | **N=662** | **N=659** |
| **TEAE (any grade)** | 653 (99) | 646 (98) |
| **Drug-related AE (any grade)** | 641 (97) | 617 (94) |
| **Drug-related severe AE (Grade ≥3)** | 525 (79) | 389 (59) |
| **Drug-related serious AE** | 240 (36) | 125 (19) |
| **WDAE (≥1 component of combination)** | 88 (13) | 105 (16) |
| **WDAE (entire treatment combination)** | 28 (4) | 22 (3) |

*ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine; AE = adverse event; BV + AVD = brentuximab vedotin plus doxorubicin, vinblastine, dacarbazine; CI = confidence interval; CR = complete remission; HR = hazard ratio; HRQoL = health-related quality of life;*

| | ECHELON-1 |
|---|---|
| *IRF = independent review facility; ITT = intention-to-treat; mPFS = modified progression-free survival; NE = not estimable; RR = relative risk; SE = standard error; TEAE = treatment-emergent adverse event; WDAE = withdrawal due to adverse event*<br>**HR < 1 favours BV + AVD treatment group*<br>*† Minimally Important Difference was specified as 10 points* | |

### 1.2.2 Additional Evidence

See Section 3, Section 4, and Section 5 for a complete summary of patient advocacy group input, Provincial Advisory Group (PAG) Input, and Registered Clinician Input, respectively.

**Patient Advocacy Group Input**

One patient input was provided by Lymphoma Canada (LC) on Brentuximab Vedotin (Adcetris) for the treatment of previously untreated patients with Stage IV HL, in combination with AVD.

From the patient's perspective, HL has a considerable physical, emotional and financial burden on the lives of patients. 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 significantly impacted patients' quality of life. When asked which aspect of their daily life was the most impacted by HL, the majority of patients stated that HL had greatly impacted their ability to work. The most common therapies for HL used by patients were ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine), radiation therapy, and autologous stem cell transplant. 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. Caregivers of HL patients also expressed financial and emotional challenges. More than half of the caregiver respondents (67%) stated that their caregiving duties had affected their ability to concentrate, contribute financially to the household, travel, and complete household chores. Six patients reported having experience with BV + AVD. The most common side-effects of BV + 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 quality of life; however, when asked to what extent they are willing to tolerate the side effects of BV + AVD, on a scale of 1-5 (1 = will not tolerate side effects; 5 = will tolerate significant side effects) 5 out of the 6 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 + 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. However, more than half of the patients (55%) stated that they would be willing to take a drug with known and potentially serious side-effects in favour of a cure or longer remission of the disease.

**Provincial Advisory Group (PAG) Input**

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- Use with other front-line combination chemotherapy
- Sequencing of other therapies downstream
- Re-treatment practicalities downstream

Economic factors:

- Potential for drug wastage
- Additional nursing and clinic resources will be required

**Registered Clinician Input**

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) for the review of Brentuximab Vedotin (Adcetris) for the treatment

of previously untreated patients with Stage IV HL, in combination with AVD. Current treatments identified by clinicians for Stage IV Hodgkin Lymphoma were ABVD and BEACOPP. Both clinician inputs stated that the patient population in the reimbursement request aligns with the need in clinical practice. The clinician from CCO, however, recommends greater flexibility with blood counts as low blood counts are most likely due to the disease and could potentially improve with treatment. The clinicians from LC stated that although Stage III and Stage IV patients are treated similarly as those in the ECHELON-1 trial, the current Health Canada approval is for Stage IV patients only. BV + AVD may be a good option for some subgroups of patients such as those over 60 or those with comorbidities, for whom the use of BEACOPP and AVD may be limited due to toxicity issues. For the subgroup of patients who are below the age of 18, the clinician from CCO noted that currently there is a lack of evidence directing the use of BV + AVD, whereas the clinicians from LC noted that the drug may be used because of similar disease biology. The clinicians from LC explained that BV + 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 + AVD would most likely be used as a complementary treatment, since there are multiple front-line options available. Patients who are ineligible for BEACOPP are a definitive subgroup of patients that would benefit from BV + AVD. Both clinician inputs noted that neutropenia and peripheral neuropathy may be potential side effects of BV + AVD, in which case, patients would likely receive G-CSF with BV + AVD. The clinicians from LC further commented that patients with pre-existing neuropathy would be unlikely to receive BV + AVD and would also likely have challenges with AVD and BEACOPP. As BV + 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 + AVD treatment would unlikely receive BV-based treatments; however, BV can be considered for patients that did not experience significant toxicity after relapsing on BV + AVD. The clinician from LC prefers the use of BV + 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, BEACOPP will be used less compared to BV + AVD.

**Summary of Supplemental Questions**

There were no supplemental questions identified for this review.

**Comparison with Other Literature**

The CADTH Clinical Guidance Panel and the CADTH Methods Team did not identify other relevant literature providing supporting information for this review.

### 1.2.3 Factors Related to Generalizability of the Evidence

Table 2 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

## Table 2: Assessment of generalizability of evidence for brentuximab vedotin for Stage IV classic Hodgkin lymphoma

| Domain | Factor | Evidence[2,4,9] | Generalizability Question | CGP Assessment of Generalizability |
|---|---|---|---|---|
| **Population** | IPFP score | The IPFP Score was a stratification factor during randomization. At baseline, most patients had IPFP Score of 2 or 3 (n=705, 53%). Baseline IPFP scores of randomized patients are as follows:<br><br>IPFP score: A+AVD N=664 / ABVD N=670<br>0 or 1: 141 (21%) / 141 (21%)<br>2 or 3: 354 (53%) / 351 (52%)<br>4 to 7: 169 (25%) / 178 (27%) | Is this representative of patients in Canadian clinical practice? | The IPFP distribution in the trial is representative of patients in Canadian clinical practice. The CGP supported generalizing the trial results to patients with the entire spectrum of IPFP scores (0 - 7). The trial included patients of the entire IPFP score spectrum and there are no data to suggest differential benefit (or not) in lower or higher scoring patients. |
| | Age | Inclusion criteria of the ECHELON-1 trial specified adults ≥ 18 years of age; the median age of enrolled patients was 36 years (range 18-83). The majority of enrolled patients (n=874; 66%) were <45 years in age. A smaller proportion (n=186, 14%) were age ≥60 years. | Is this representative of adult patients in Canadian clinical practice? | The age distribution of patients in the trial is respective of adult patients in Canadian clinical practice. Patients <18 years of age were excluded from the ECHELON-1 trial. The CGP agreed that there is currently insufficient evidence to make an informed recommendation on the use of BV + AVD in patients <18 years of age.<br>The CGP agreed that the trial results can be generalized to patients (>60 years of age) given the overall manageable safety profile of BV + AVD. |
| | Organ dysfunction | Inclusion criteria of ECHELON-1 study required patients to have adequate liver and renal function, as well as adequate hematological lab values (i.e., ANC ≥1.5 x $10^9$/L, PLT ≥75 x $10^9$/L, Hg ≥80g/L) within 7 days prior to receiving first dose of study drug. | Does the exclusion of patients with organ dysfunction or suboptimal hematological lab values limit the interpretation of the trial results with respect to the target population? | Given the generally tolerable safety profile of BV + AVD, the CGP suggests it is up to the discretion of the treating physician to apply some flexibility in terms of using BV + AVD in patients with abnormal lab parameters different than those outlined in the ECHELON-1 trial. |

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence[2,4,9]</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td rowspan="2">Intervention</td><td>Dose, schedule, and treatment approach</td><td>Patients in both groups received IV infusions on Days 1 and 15 of a 28-day cycle. Treatment was continued up to a maximum of six cycles.<br><br>A+AVD was administered in sequential order:<br>A: Doxorubicin 25 mg/m$^2$ IV infusion<br>V: Vinblastine 6 mg/m$^2$ IV infusion<br>D: Dacarbazine 375 mg/m$^2$ IV infusion<br>A: Brentuximab vedotin 1.2 mg/kg IV infusion over approximately 30 minutes<br><br>The brentuximab vedotin dose was calculated based on actual weight and capped at 100kg.</td><td>Are the trial dosages generalizable to patients in Ontario? Across Canada?</td><td>The CGP agreed that the doses used in the trial reflects the standard dose schedules used in Canada.</td></tr>
<tr><td>PET scan guided strategies</td><td>In the ECHELON-1 trial, treatment regimens were not adapted based on PET-response. Treatment with ABVD consisted of doxorubicin, bleomycin, vinblastine, dacarbazine administered as IV infusions on Days 1 and 15 of a 28-day cycle. Treatment was continued up to a maximum of six cycles.<br><br>A PET scan was performed after 2 cycles of treatment (PET2); if results showed a Deauville score of 5, physicians had the option of switching the patient's treatment to an alternative regimen. Breakdown of Deauville score with PET2 is as follows:<br><br><table><tr><th>Deauville score</th><th>A+AVD N=664</th><th>ABVD N=670</th></tr><tr><td>1</td><td>435 (66%)</td><td>414 (62%)</td></tr><tr><td>2</td><td>131 (20%)</td><td>133 (20%)</td></tr><tr><td>3</td><td>22 (3%)</td><td>30 (4%)</td></tr><tr><td>4</td><td>26 (4%)</td><td>28 (4%)</td></tr><tr><td>5</td><td>21 (3%)</td><td>30 (4%)</td></tr><tr><td colspan="3">Results were unavailable for 29 (4%) and 35 (5%) patients in the A+AVD and ABVD groups, respectively.</td></tr></table><br>Treatment was switched to an alternative regimen due to a Deauville score of 5 in four patients in the ABVD group (and one patient in the A+AVD group).</td><td>Are the trial results generalizable to the Canadian clinical practice, where PET-guided strategies are commonly used?</td><td>PET-guided treatment is emerging as a popular approach to treatment of advanced cHL. Although an interim PET-guided treatment approach was not included in the ECHELON-1 trial in either of the study groups, the CGP supports BV + AVD as an option in the Canadian context, in which strategies currently include frontline ABVD, PET-guided strategies, and rarely frontline eBEACOPP. Further, the CGP noted that the PET-guided approach emerged based on ABVD or escalated BEACOPP frontline therapy. The applicability of the PET-guided approach with BV + AVD as front-line therapy is out of the scope of this review. There is currently insufficient evidence to guide the use of interim PET imaging to risk-stratify and adapt therapies in patients who have started on BV + AVD therapy.</td></tr>
<tr><td>Comparator</td><td>Standard of care</td><td>In the ECHELON-1 trial, ABVD x 6 cycles was chosen as the comparator.</td><td>Is the comparator a relevant current standard of care</td><td>The CGP agreed with the Provincial Advisory Group (PAG), that ABVD is the main standard of care in Canada and thus a relevant comparator.</td></tr>
</table>

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence[2,4,9]</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td></td><td></td><td></td><td>in Canada?</td><td></td></tr>
<tr><td>Setting</td><td>Ethnicity and countries participating in the trial</td><td>The ECHELON-1 trial was conducted in 218 sites in 21 countries, enrolling patients from the America (n=523, 39%), Europe (n=669, 50%), and Asia (n=142, 11%). There were 60 patients treated in Canada who were enrolled in the trial, representing the provinces of British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Quebec, and Nova Scotia.<br>There were 497 patients enrolled from North America. According to subgroup analysis, the mPFS HR for North America was 0.60 (95% CI, 0.40 to 0.90). HR for different clinical stages are as follows:<br>Stage III: 0.64 (95% CI, 0.33 to 1.24)<br>Stage IV: 0.55 (95% CI, 0.33 to 0.94)<br>The ethnicities of patients in the overall ITT population were as follows:
<table>
<tr><th>Race</th><th>A+AVD N=664</th><th>ABVD N=670</th></tr>
<tr><td>White</td><td>560 (84%)</td><td>554 (83%)</td></tr>
<tr><td>Asian</td><td>56 (8%)</td><td>57 (9%)</td></tr>
<tr><td>Black or African American</td><td>20 (3%)</td><td>25 (4%)</td></tr>
<tr><td>Other</td><td>18 (3%)</td><td>17 (3%)</td></tr>
<tr><td>Not reported</td><td>10 (2%)</td><td>17 (3%)</td></tr>
</table>
Specific to the North American subgroup, the ethnicities were as follows:
<table>
<tr><th>Race</th><th>A+AVD N=250</th><th>ABVD N=247</th></tr>
<tr><td>White</td><td>213 (85%)</td><td>204 (83%)</td></tr>
<tr><td>Black or African American</td><td>15 (6%)</td><td>16 (6%)</td></tr>
<tr><td>Not reported</td><td>9 (4%)</td><td>15 (6%)</td></tr>
<tr><td>Asian</td><td>7 (3%)</td><td>7 (3%)</td></tr>
<tr><td>Other</td><td>6 (2%)</td><td>5 (2%)</td></tr>
</table></td><td>Most enrolled patients were from Europe; is there a known difference in effect based on ethnicity that might yield a different result in a Canadian setting?<br>Are there any known difference in the practice patterns between Canada and other countries that the trial was conducted in?</td><td>The trial results are fully applicable to the Canadian landscape. The CGP does not expect different treatment effect based on ethnicity or different disease management practices across countries.</td></tr>
</table>

### 1.2.4 Interpretation

**Burden of Illness and Need**

According to 2020 Canadian Cancer Statistics, Hodgkin Lymphoma represents approximately 0.4% of all newly diagnosed cancers, 0.1% of cancer-related deaths, and totals approximately 1000 new cases and 100 deaths each year in Canada.[10] Of newly diagnosed patients during 2011 to 2015, 23.3% had Stage III disease and 22.7% had Stage IV disease.[11] Prognosis of HL varies and depends on numerous factors, including stage of disease; the relative 5-year overall survival is 80% and 65% in patients with Stage III and Stage IV disease, respectively.[12,13]

Advanced stage disease typically includes patients with Stage III or IV disease, and patients in both stages are managed similarly. In Canada, the standard regimen for advanced disease is ABVD for up to six cycles. Classic HL is generally regarded as a curable disease; however, despite the high complete remission rates with current standard of treatment, up to 25% of patients experience disease progression and require subsequent treatment, including high dose therapy and autologous stem cell transplantation (ASCT).[14,15] In patients with advanced disease, overall survival with ABVD is approximately 90% at four years and 55% at 10 years, though some studies show higher rates, for example 85% overall survival at 10 years.

In a small subset of young, healthy patients with high-risk disease, escalated BEACOPP may be an option. Although this combination may have an advantage over ABVD for progression-free survival, improved overall survival has not been definitively demonstrated and the unfavourable adverse effect profile, including secondary malignancy, precludes its widespread use.[14,16] ABVD is also not void of toxicity, and some patients may have difficulty tolerating the combination. Thus, the risk of relapse combined with concerns over acute and long-term adverse effects, such as bleomycin-related toxicity, have led to identification of new treatments and approaches. One example is PET-adapted therapy, which uses interim PET-scan results to direct treatment decisions; individuals with high risk disease based on interim PET may undergo treatment intensification whereas patients with lower risk disease might be eligible for treatment de-escalation. Uptake of this strategy may vary by region but is being adopted by an increasing number of treatment centres across Canada. Therefore, there is still need in advanced cHL for more effective therapies with tolerable toxicity and the potential for long-term remission and cure.

The CGP agreed that BV + AVD with its potential for long term cure and overall tolerable safety profile addresses an unmet need in previously untreated patients with advanced cHL. Upon relapse after BV + AVD, the likelihood of cure diminishes significantly with each subsequent line of therapy. While some patients may be candidates for ASCT after relapse on BV + AVD, treatment options for patients who are ineligible to receive ASCT are with palliative intent only. In general, patients who are at greater risk of toxicity from current frontline treatment such as bleomycin (e.g., older with comorbidities) may not be eligible for, or be at risk of complications associated with subsequent treatment such as ASCT, thus underscoring the need for effective first-line treatment.[16]

The CGP noted that at this time there is insufficient evidence from the trial on whether patients on BV + AVD will be less or more likely to receive ASCT. Also, no conclusions can be drawn about the outcomes of ASCT after BV + AVD from this trial.

**Effectiveness**

The efficacy of BV + AVD in the first-line treatment of advanced cHL was demonstrated in the ECHELON-1 trial, which randomized 1334 adult patients with previously untreated Stage III or IV cHL. Median age of patients was 36 years. There were 36% and 64% of patients with Stage III and IV disease in the BV + AVD group and 37% and 63% of patient with Stage III and IV disease in the ABVD group. The ECHEON-1 trial demonstrated that mPFS, the primary outcome of the trial, was clinically and statistically significant in favour of BV + AVD compared to ABVD. At median follow-up of 24.6 months, median mPFS had not been reached. Two-year mPFS was higher in patients treated with BV + AVD compared to ABVD (82.1% vs. 77.2% respectively; absolute difference of 4.9%), with HR of 0.77 (95% CI, 0.60 to 0.98; p=0.04) for progression, death, or modified progression.

The primary endpoint (mPFS) selected by investigators is novel and has not been validated in the published literature and the strength of the association between mPFS and OS 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. The CGP agreed that while using mPFS makes cross-trial comparisons (to trials reporting on traditional PFS) more difficult and may be

more prone to subjective bias (i.e., up to the discretion of treating clinicians to radiate or not to radiate incomplete responders), mPFS results were numerically more conservative than those seen in the exploratory analyses of PFS. CGP felt comfortable using mPFS for medical decision-making and noted that it is a clinically meaningful endpoint in this patient population as it appropriately reflects the curative intent of frontline treatment by identifying patients who receive additional treatment due to noncomplete response.

The mPFS benefit was not seen in all pre-specified exploratory subgroups. Although hazard ratios for subgroup results suggested that BV + AVD was numerically more favourable compared to ABVD, confidence intervals crossed 1.0 for most subgroups. The risk reduction in patients with Stage IV disease was 28.9% with BV + AVD over ABVD treatment, with unstratified HR of 0.71 (95% CI, 0.53 to 0.96). However, in patients with Stage III disease, a 7.8% risk reduction in mPFS events, favouring BV + AVD was seen, with unstratified HR of 0.92 (95% CI, 0.6 to 1.42), which indicates a smaller magnitude of benefit than in the ITT population. Of note, the CGP cautioned against drawing specific conclusions related to the treatment benefit within exploratory subgroups. The ECHELON-1 trial was designed to determine if there is a benefit in the ITT population (including Stages III & IV) and not designed to test specific hypotheses for disease stage subgroups. An updated exploratory analysis of PFS at three and four years of follow-up showed 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. The CGP noted that PFS at 4 years is highly suggestive of cure in this disease. Late relapses beyond 4 years occur rarely. The 3-year PFS rate was higher in patients treated with BV + AVD compared to ABVD (83.1% vs. 76.0% respectively; absolute difference of 7.1%), with HR of 0.70 (95% CI, 0.55 to 0.90). At four-year follow up the PFS rate was consistently higher in patients treated with BV + AVD compared to ABVD (81.7% vs. 75.1% respectively; absolute difference of 6.6%), with HR of 0.69 (95% CI, 0.54 to 0.88). After randomized treatment, a high proportion of patients in both treatment groups had achieved complete remission (73% and 70% for BV + AVD and ABVD groups, respectively), which was maintained with less than 5% of patients in each treatment group receiving subsequent treatment due to disease progression. The CGP noted that complete remission rate has not proven to be a valid surrogate for more meaningful outcomes, such as PFS or OS in the present context. Therefore survival outcomes guide treatment selection rather than response outcomes in this setting. At the time of data cut-off, overall survival data was still immature but showed a potential trend towards benefit with BV + AVD (HR=0.73; 95% CI, 0.45 to 1.18, p=0.20).

The study follow-up is planned for 10 years follow-up time; such long-term data are expected to provide more robust results to help characterize the risks and benefits of this combination, and further guide treatment decisions.[2]

**Safety**

No new safety concerns were identified in the trial. Overall, a higher incidence of known adverse effects (AEs) and dose modifications were seen in patients treated with BV + AVD compared to ABVD. Although the rate of discontinuation of the entire combination was similar between the two groups, TEAEs resulting in discontinuation of a drug component in the treatment was greater in the ABVD group (16% vs. 13% in BV + AVD). The AE profiles of each treatment combination was distinct, with the differences seen mainly due to the bleomycin and BV components (e.g., greater pulmonary toxicity with ABVD, more peripheral neuropathy and neutropenia with BV + AVD).

A higher incidence of severe TEAEs (Grade ≥ 3), serious TEAEs, and drug-related adverse effects were reported in patients treated with BV + AVD. In particular, neutropenia, febrile neutropenia, and peripheral neuropathy were reported in greater number of patients who received BV + AVD than ABVD, and a component of the BV + AVD treatment combination was discontinued most frequently due to similar reasons. Implementation of G-CSF prophylaxis in patients receiving BV + AVD resulted in reduction of neutropenia and infection. Of 442 patients who developed peripheral neuropathy while receiving BV + AVD, 67% of patients had experienced either resolution or improvement by the last follow-up date. Most remaining cases were either of Grade 1 or 2 in severity.[2] Four-year follow-up data showed that most patients (68% and 76% in BV + AVD and ABVD, respectively) had experienced complete resolution. In general, these side effects are as expected for BV + AVD; although event rates were high (drug-related Grade ≥ 3 AE, ITT population: 79% BV + AVD vs 59% ABVD), mitigation of common TEAEs such as neutropenia was demonstrated by administering G-CSF prophylaxis, and improvement/resolution of peripheral neuropathy over time is reassuring.

Similar pattern of drug-related AEs was seen in patients with Stage III and IV disease compared to the overall population. However, in the BV + AVD treatment group, patients with Stage IV disease had lower incidence of serious AE, treatment-related serious AE, and AE resulting in study drug discontinuation compared to those with baseline Stage III cHL, suggesting that patients with Stage III

disease had experienced slightly greater toxicity. The CGP cautioned against drawing specific conclusions from exploratory safety analyses by subgroups and noted that there appears to be no intuitive explanation for the increased toxicities observed in patients with Stage III disease compared with Stage IV disease.

With respect to exploratory quality of life data, BV + AVD did not appear to significantly affect quality of life with no clinically meaningful difference noted between the two study groups. Though, not clinically significantly different, QOL scores were slightly worse with BV + AVD compared with ABVD during the treatment period which may be reflective of the higher frequency of severe TEAEs (≥ Grade 3) and serious adverse events observed in patients who received BV + AVD.

The CGP agreed with the clinicians providing input for this submission that the improvement in PFS outweighs the safety concerns. This was echoed by patient input suggesting that the majority of patients who have been treated with BV + AVD considered that the longer remission or cure outweighed the difficult side effects, and all were willing take this drug again if the physician thought it was their best option.

## 1.3 Conclusions

The Clinical Guidance Panel concluded that there is a net clinical benefit to BV in combination with AVD compared with ABVD in previously untreated patients with Stage IV HL. This conclusion is based on evidence from a pre-defined exploratory subgroup analysis from a high-quality randomized placebo-controlled trial (ECHELON-1). The overall trial results demonstrated a clinically and statistically significant benefit in mPFS of BV + AVD over ABVD. The subgroup results for mPFS for Stage IV disease suggested a clinically significant improvement with greater benefit than observed in the overall study results. Long-term analyses continue to demonstrate a preserved PFS (PFS was an exploratory outcome in the ECHELON-1 trial) benefit associated with BV + AVD. The trial data on OS remain immature but demonstrate a positive trend in favour of BV + AVD, however, it should be noted that subsequent OS analysis may be confounded by post-trial treatment administration, including BV. The CGP agreed that mPFS is a clinically meaningful endpoint as it is indicative of the curative potential for BV + AVD in this setting. Upon relapse after BV + AVD, the likelihood of cure diminishes dramatically with each subsequent line of therapy and only a proportion of patients may be candidates for ASCT after relapse on BV + AVD; treatment options for patients who are ineligible to receive ASCT are with palliative intent only. Additionally, the improvements in mPFS observed with BV + AVD are important in this patient population as clinically Stage IV disease has been traditionally considered at high risk for disease recurrence, due to the high stage of disease (i.e. tumour burden) and high IPFP risk factors (score 4-7) at presentation.

The safety and QOL profile of BV + AVD is acceptable with no new safety concerns. Patients treated with BV + AVD experienced severe or serious adverse events more frequently; however, the degree of treatment-related toxicity was considered generally acceptable, especially with primary prophylaxis using G-CSF. Furthermore, pulmonary toxicity associated with bleomycin which can have devastating effects on patients is avoided with BV + AVD. The CGP agreed that BV has previously been studied in patients with HL. Phase II and III trials post-ASCT demonstrate a high degree of efficacy and acceptable and predictable toxicity.

In making this conclusion, the Clinical Guidance Panel (CGP) also considered that:

- The CGP noted that Canadian clinicians universally treat Stage III and IV the same and therefore strongly supported generalizing the trial results to patients with Stage III disease. The CADTH reimbursement request aligns with the Health Canada (HC) approved indication, which is limited to patients with Stage IV disease. The CGP noted that the ECHELON-1 trial was designed to determine if there is a benefit in the ITT population (including stages III & IV) and not designed to test specific hypotheses for disease stage subgroups. Furthermore, since the HC approval, updated three-and four-year follow-up data of the exploratory outcome PFS per investigator have been published that show a preservation of benefit (i.e., K-M curves between study groups did not cross) in the ITT population and Stage III disease subgroup results consistent with the overall study results. Additionally, CD30 expression is the target for the mechanism of action of BV and there is no apparent biological rationale to assume that outcomes of BV + AVD therapy would be different between subtypes of Stage III & IV disease.
- Based on the CGP clinical opinion, it is reasonable to anticipate that if BV + AVD becomes available for the requested target population, it will be the preferred option to replace ABVD alone as the standard of care in first-line treatment, because of its prolonged mPFS and potential for cure with a manageable toxicity profile. Very rarely patients present with significant pre-existing peripheral neuropathy in which case ABVD would likely be favoured.
- Removing the risk of bleomycin-associated pulmonary toxicity (which can be severe, permanent and even fatal) while improving efficacy is an important advancement in first-line therapy for patients with advanced cHL.

PET-guided treatment is emerging as a popular approach to treatment of advanced cHL. The PET-guided treatment approach was not included in the ECHELON-1 trial, as the start of this trial preceded current recommendations for PET-adapted strategies. Further, the CGP noted that the PET-guided approach emerged based on ABVD or escalated BEACOPP frontline therapy. The applicability of the PET-guided approach with BV + AVD as front-line therapy is out of the scope of this review. There is currently insufficient evidence to guide the use of interim PET imaging to risk-stratify and adapt therapies in patients who have started on BV + AVD therapy.

## Table 3: CADTH Clinical Guidance Panel Response to Provincial Advisory Group Implementation Questions

| PAG Implementation Questions | CGP Response |
|---|---|
| **Eligible Patient Population** | |
| PAG is seeking guidance on whether the following patients would be eligible for treatment with BV + AVD: | |
| • Patients less than 18 years of age | • Patients <18 years of age were excluded from the ECHELON-1 trial. The CGP agreed that there is currently insufficient evidence to make an informed recommendation on the use of BV + AVD in patients <18 years of age. |
| • Patients with an ECOG performance score greater than 2 | • The benefit for patients with ECOG PS > 2 cannot be formally concluded from the ECHELON-1 trial as these patients were excluded. However, it would be reasonable to offer BV in combination with AVD in situations in which the patients' poor performance status (i.e., 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 | • The CGP supported generalizing the trial results to patients who have Stage III disease for the following reasons:<br>(1) The ECHELON-1 trial was designed to determine if there is a benefit in the ITT population (including Stages III & IV) and not designed to test specific hypotheses for disease stage subgroups.<br>(2) CD30-expression is the target for the mechanism of action of BV and there is no apparent biological rationale to assume that outcomes of BV + AVD therapy would be different between subtypes of Stage III & IV disease.<br>(3) Three- and four-year follow-up data of the exploratory outcome PFS per investigator showed a preservation of benefit (i.e., K-M curves between study groups did not cross) in the ITT population. Subgroup results for Stage III disease show consistent results with the overall study results.<br>(4) The CGP noted that no new safety concerns were identified in the trial. Among the most commonly reported TEAEs in both regimens were neutropenia and peripheral sensory neuropathy, though incidence was higher in the BV + AVD group. At 4 years of follow-up, most residual peripheral neuropathy was low grade (59% Grade 1; 30% Grade 2).<br>• The CGP noted that patients with Stage IIb disease were not included in the ECHELON-1 trial. However, 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. Despite the insufficient evidence, the CGP does support generalizing the trial results to patients with Stage IIb disease being otherwise treated with protocols intended for advanced stage HL. |

| PAG Implementation Questions | CGP Response |
|---|---|
| • Nodular lymphocyte-predominant HL | • The CGP agreed 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, is not expected to respond to BV. |
| • Patients with cardiovascular conditions | • Patients with pre-existing cardiovascular disease were excluded from the trial. The CGP agreed that there is insufficient evidence to generalize the trial results to these patients. |
| • Patients with CNS involvement and PML symptoms | • Patients with cerebral or meningeal disease, including signs or symptoms of PML were excluded from the trial. The CGP agreed that there is insufficient evidence to generalize the trial results to these patients. |
| If recommended for reimbursement, PAG noted that patients who have initiated ABVD or BEACOPP would need to be addressed on a time-limited basis. | The CGP noted that in the absence of sufficient evidence to guide this decision, it would seem reasonable to offer BV + AVD to patients who have initiated ABVD on a time-limited basis. However, the CGP noted that patients who have initiated BEACOPP should not be offered BV + AVD on a time-limited basis. |
| 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. | The CGP felt 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. | The CGP noted that there are no data to support the generalizability of treatment benefit with BV + AVD to patients with earlier stages of disease or other lines of therapy. |
| With regards to combining BV with chemotherapies other than AVD, PAG is seeking guidance on:<br>• Substituting etoposide for patients unable to receive doxorubicin.<br>• Combining BV with BEACOPP instead of AVD<br>• Using BV to replace bleomycin in BEACOPP? | The CGP does not support generalizing the trial results to BV in combination with chemotherapy regiments other than AVD. The CGP noted that there is currently insufficient evidence regarding the safety profile of BV when combining with other combination 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 | pERC agreed with the CGP that the ECHELON-1 trial criteria used for treatment discontinuation, i.e., 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 |

| PAG Implementation Questions | CGP Response |
|---|---|
| imaging is used and how often patients are scanned during and after treatment? | not common practice in Canada. Clinicians may, however, advise 1-2 imaging scans in the first 3-12 months after full completion of therapy. |
| Additional resources (e.g., nursing and clinic visits) are required to monitor and treat infusion-related reactions and adverse events (e.g. diarrhea, neutropenia/febrile neutropenia, and peripheral neuropathy) as well as monitor complete blood count. PAG noted that the rates of neutropenia are higher with BV + AVD compared with ABVD. | The CGP did not anticipate a significant increase in resource utilization for monitoring. The CGP noted that additional monitoring will not be required, and febrile neutropenia can safely be managed as an outpatient. |
| 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.<br><br>If BV + 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? | Overall, the CGP supported the statement in the Health Canada product monograph that primary prophylaxis with G-CSF is recommended beginning of Cycle 1 for all patients who receive treatment with BV + AVD. The CGP agreed that G-CSF may entail an additional cost. 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 + AVD and are at high risk of febrile neutropenia. |
| **Sequencing and Priority of Treatment** | |
| What circumstances would drive the preference to prescribe BV + AVD versus ABVD or BEACOPP. | In general, the CGP anticipated a high uptake of and strong preference for the use of BV + AVD over ABVD. Furthermore, patients who have a high-risk or concern for bleomycin lung toxicity would likely strongly prefer BV + AVD. A possible reason for choosing ABVD over BV + AVD may include pre-existing peripheral neuropathy. BEACOPP is rarely used first line, but for patients with an increased number of IPS risk factors, there may be a preference to use more intense approaches (BEACOPP) or PET-based approaches. |
| CGP please clarify possible sequencing of treatments after progression with BV including allogeneic stem cell transplant, immunotherapies and potential re-treatment with BV. | In the absence of sufficient evidence to guide sequencing of treatments after progression on BV + AVD, the CGP noted that possible sequencing options upon early relapse after BV + AVD include gemcitabine, dexamethasone, and cisplatin (GDP) followed by autologous stem cell transplant (ASCT) ± BV consolidation. Possible treatment option upon later relapse (if > 12 months since last exposure to BV) include re-treatment with BV followed by PD-1 inhibitor therapy. Allogeneic SCT is rarely use in this disease. For patients who are transplant ineligible, a PD-1 inhibitor may be the next line after BV + AVD failure. |
| PAG also seeks guidance on the effectiveness and timing of re-treatment with BV in patients who progress or relapse after downstream therapies. | The CGP noted that in the absence of sufficient evidence to guide this decision, it would seem unlikely that patients who are actively progressing on BV + AVD would benefit from re-treatment with BV (or consolidation post-SCT with BV). However, it would seem reasonable to offer re-treatment with BV or BV consolidation treatment to patients who respond to BV + AVD (and have a reasonable response duration [e.g., >12 months]). |
| Evidence for continuing brentuximab as a single agent for high risk patients after completion of BV + AVD. | The CGP noted that there is insufficient evidence to make a recommendation regarding continuing brentuximab as a single agent for high risk patients after completion of BV + AVD. |

PAG = Provincial Advisory Group, CGP = Clinical Guidance Panel

# 2 Background Clinical Information

## 2.1 Description of the Condition

Classic Hodgkin lymphoma (cHL) is an uncommon but distinct type of lymphoma with a bimodal age distribution. Diagnosis typically occurs between 15 to 30 years of age and also over the age of 55 years, though it can also occur in children.[12,14] cHL is one of two categories of Hodgkin lymphoma (HL); it accounts for 95% of HL cases and is characterized by the presence of CD30+ Reed-Sternberg cells.[14] Subtypes of cHL include nodular sclerosis, mixed cellularity, lymphocyte-rich, and lymphocyte-depleted. Nodular lymphocyte-predominant HL, the second category of HL, lacks the characteristic Reed-Sternberg cells and comprises only a minority (5%) of all patients with HL.[14] In 2020, it is estimated that approximately 1000 new cases of Hodgkin lymphoma will be diagnosed in Canada, translating to 2.6 cases per 100,000. A slightly higher incidence is estimated in males (2.9 per 100,000) compared to females (2.3 per 100,000). It is further projected that approximately 100 Canadians will die from HL this year.[10]

Of patients newly diagnosed with HL in Canada during 2011 to 2015, 23.3% had Stage III disease and 22.7% had Stage IV disease.[11] Overall, the estimated 5-year survival for patients diagnosed with HL is 86%; however, prognosis can vary depending on numerous factors, including stage of disease.[13] Accordingly, the average 5-year relative overall survival is 90% for patients in Stage I and II, whereas this decreases to 80% in patients with Stage III and 65% in patients with Stage IV disease.[12] Survival in advanced HL is also dependent on additional risk factors, as encompassed in the International Prognostic Score (IPS). Based on seven unfavourable clinical parameters (i.e., Stage IV disease, age ≥ 45 years, male sex, hemoglobin < 105 g/L, albumin < 40 g/L, white blood cell count ≥ 15 x $10^9$/L and lymphocyte count < 0.6 x $10^9$/L or < 8% of differential), overall survival decreases with greater number of factors and higher IPS. The 5-year overall survival ranges from 98% in patients with IPS of 0, to 67% in patients with IPS of 5 or greater.[17]

## 2.2 Accepted Clinical Practice

Primary treatment for advanced-stage cHL involves combination chemotherapy regimens, with radiation therapy considered in those with active residual disease or in some circumstances with initial bulk.[14,18] Advanced stage disease typically includes patients with Stage III or IV disease, though patients with earlier stage disease and unfavourable risk factors (e.g., bulky disease, extranodal sites, elevated erythrocyte sedimentation rate, and/or constitutional “B” symptoms) may also be treated with an advanced-stage strategy.[14,16] In Canada, the standard regimen for advance disease is ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) for six cycles. In a small subset of young, healthy patients with high-risk disease (e.g., IPS ≥4), escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) for up to 6 cycles may be given. Involved field radiation may be administered after chemotherapy to localized PET-positive residual disease (e.g., ≥ 2.0 cm) and may be considered after ABVD for initially bulky sites.[16] Although the escalated BEACOPP regimen appear to have an advantage over ABVD for progression-free survival, improved overall survival has not been definitively demonstrated and the adverse effect profile, including secondary malignancy, precludes its widespread use.[14,16]

Increasingly, fluorodeoxyglucose-positron emission tomography (FDG-PET) scanning is being used to direct treatment decisions in those with early and advanced HL, with the goal of limiting toxicities in those with favourable response following 2 cycles of therapy by de-escalation of therapy, and improving outcome through treatment intensification for those with less than complete response.[16] For example, regimens based on the RATHL (Response-Adapted Therapy in Advanced Hodgkin Lymphoma) trial that initiate PET-directed therapy with ABVD allows potential removal of bleomycin after two cycles, thereby reducing risk of pulmonary toxicity.[14] The RATHL trial compared ABVD to de-escalated AVD regimen for the remaining four cycles after a negative interim PET scan, and resulted in no significant difference in rates of 3-year PFS (86% ABVD vs. 84% AVD) and OS (97% ABVD vs. 98% AVD), with reduced incidence of TEAEs such as pulmonary toxicity.[15] If inadequate response is seen after two cycles of treatment, as measured by Deauville criteria (i.e., positive PET scan), the regimen can be intensified to escalated BEACOPP in eligible patients (i.e., age < 60-70 years, ECOG 0-2, without major comorbidities, and the fertility implications are acceptable).[14,16] With more treatment centres adopting PET-adapted therapy, guidelines have also been updated to include, and in some cases prefer, this approach.[14,16,18,19] However, there may be interprovincial, inter-institutional and interpractitioner variability in funding and approaches to FDG-PET

scanning. For example, there has not been universal adoption of PET-adapted escalation of therapy based on concern of long-term toxicity and the lack of convincing survival benefit.

cHL is generally regarded as a curable disease; however, despite the high complete remission rates with current ABVD chemotherapy (>80% for advanced stage disease), up to 25% of patients experience disease progression and require subsequent treatment, including high-dose chemotherapy and autologous stem cell transplantation (ASCT).[14,15] In patients with advanced disease, overall survival with ABVD is approximately 90% at four years and 55% at 10 years, though some studies show higher rates, for example 85% overall survival at 10 years.[15,20] To further improve survival as well as reduce acute and long-term toxicity associated with current therapies, numerous treatment approaches and modalities are being been explored in this advanced setting.[21] Brentuximab vedotin (BV), an anti-CD30 antibody-drug conjugate, is one agent that has been investigated or is currently undergoing trials in combination with different chemotherapy regimens. The ECHELON-1 trial, which forms the basis of this review, compares BV in combination with AVD (doxorubicin, vinblastine, dacarbazine) to ABVD. In the Phase III HD21 trial, BV is being investigated as part of a combination with etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone (BrECADD) and compared to escalated BEACOPP (clinicaltrials.gov NCT02661503).[22] Immune checkpoint inhibitors, such as nivolumab and pembrolizumab, are also being explored for frontline treatment of advanced cHL.[21] For example, nivolumab is being studied in a head-to-head comparison to BV when given in combination with AVD in an ongoing Phase III study which also includes pediatric patients 12 years and older (NCT03907488).[23] BV in combination with AVEPC (doxorubicin, vincristine, etoposide, prednisone, cyclophosphamide) is also being compared to ABVE-PC (doxorubicin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide) in the pediatric population (NCT02166463).[24]

Several earlier phase trials (e.g., Phase II) are also underway to better characterize the role of BV in different treatment approaches and patient populations. For example, a PET-adapted strategy is being investigated in the Phase II COBRA study which compares the combination of BV with either AVD or ECADD (etoposide, cyclophosphamide, doxorubicin, dacarbazine) after one cycle of BV + AVD (NCT03517137).[25] Several studies of BV in pediatric patients with advanced cHL are in also in early phases and explores various combinations. For example, one Phase II trial is investigating BV plus AVD for up to six cycles in children 5-17 years (NCT02979522).[26] Response-adapted therapy is also being investigated in the cHOD17 trial, which is enrolling patients 25 years or younger with high-risk disease to two cycles of AEPA (brentuximab, etoposide, prednisone, doxorubicin) and 4 cycles of CAPDac (cyclophosphamide, brentuximab, prednisone, dacarbazine), with treatment adjusted after 2 cycles of therapy (NCT03755804).[27] Role of BV in treatment of older patients with cHL is also being explored, such as in the Phase 1/2 HALO study where BV in combination with bendumustine for up to six cycles is being administered to patients 60-80 years of age (NCT02467946).[28] BV in combination with nivolumab is also being studied in patients over 60 years of age for first-line treatment of cHL (NCT02758717).[29] Regarding this older patient population, a small Phase II trial published in 2018 by Evens et al., investigated BV given sequentially before and after six cycles of AVD (i.e., as lead-in and consolidation) in patients 60 years or older with Stage II to IV cHL.[30] Results showed that complete remission rates in the ITT population after BV lead-in and six cycles of ABVD was 83% (40 of 48 patients), and 85% (41 of 48 patients) after consolidation therapy with BV. At a median follow-up of 23 months, 2-year PFS was 84% (95% CI, 69% to 92%), and OS was 93% (95% CI, 80% to 98%). However, many patients were unable to complete the full study treatment (i.e., 23% did not receive full six cycles of AVD and 48% did not receive complete brentuximab consolidation treatment); study authors comment that future investigations to reduce treatment intensity and maintain outcomes should be performed.[30] Overall, there are numerous ongoing studies involving BV for the treatment of cHL in various patient populations and as part of different strategies; results from these studies may further define the place in therapy of this targeted therapy.

Brentuximab vedotin has been issued marketing authorization without conditions for the present indication under review: the treatment of previously untreated patients with Stage IV Hodgkin lymphoma (HL) in combination with doxorubicin, vinblastine, and dacarbazine (AVD). The Sponsor noted that their original application to Health Canada was for the ITT population (including Stage III and Stage IV patients). Health Canada's final decision was based on the totality of evidence showing that the benefit of BV + AVD was most substantial in patients with Stage IV disease. It appears that a precautionary approach was considered due to uncertainties regarding efficacy (including inconsistency in observed mPFS benefit between Stage III and IV subgroups, immature OS data, and use of surrogate endpoint); 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.

In addition to the indication under current review (i.e., for previously untreated patients with Stage IV disease), brentuximab vedotin, is also approved for two indications in HL: 1) consolidation treatment post-ASCT in patients with increased risk of relapse or progression; and 2) treatment after failure of ASCT or after failure of two or more multi-agent chemotherapy regimens in patients who are not candidates for ASCT.[1] In most provinces, BV has become the treatment of choice as initial therapy for relapse after ASCT because of its favourable toxicity profile. Funding for BV for those who are not candidates for ASCT because of age, comorbidities or refractoriness to salvage therapy is not uniform across Canada and results in a significant treatment gap for this subgroup of patients in most provinces.

Furthermore, the CGP noted that it is important to recognize that a majority of clinical cancer drug trials do not include a proportionate number of patients identified as a race/ethnicity other than White, e.g., Black, Indigenous, or Asian. Therefore, the race/ethnicity distributions in trial populations often do not accurately match the racial/ethnic makeup of the Canadian population. The CGP wishes to acknowledge the disproportionate representation of minority demographic groups and the need for systemic change to actively facilitate proportionate inclusion of such individuals in clinical cancer drug trials.

# 3 Summary of Patient Advocacy Group Input

One patient input was provided by Lymphoma Canada (LC) on Brentuximab Vedotin (Adcetris) for the treatment of previously untreated patients with Stage IV HL, in combination with AVD.

Lymphoma Canada collected input from Hodgkin Lymphoma patients and caregivers through two online surveys. The responses to these surveys were collected from June 5th – 30th, 2017. Responses from an additional survey were collected from March 25th – April 10th, 2020 for patients who have experience with BV + AVD. The links to these surveys were emailed to patients and caregivers registered on the LC database and were also disseminated via LC Twitter and Facebook accounts, as well as through HL patient forums, other HL-dedicated social media pages and groups, and contacts of international lymphoma organizations. The surveys consisted of multiple-choice questions, rating scale questions, and open-ended questions. A total of 103 respondents provided input, 88 (85%) of whom were patients and 15 (15%) of whom were caregivers. The majority (47; 57%) of the respondents were from Canada (Table 4). Five of the six respondents who had experience with BV + AVD, were from Canada and one was from the USA. Out of the 67 patient respondents, those with and without BV + AVD experience, who provided their gender (Table 5) the majority were female (46, 69%). Out of the 67 patient respondents who stated their age (Table 5), 35 (52%) were between the ages of 20-39, and 21 (31%) were between the ages of 40-59. Respondents were not asked to identify their stage of disease.

## Table 4: Respondents by Country

| Respondents | Canada | USA | United Kingdom | European Union | Other | Skipped | Total |
|---|---|---|---|---|---|---|---|
| Patients with BV + AVD experience | 5 | 1 | 0 | 0 | 0 | 0 | **6** |
| Patients without BV + AVD experience | 37 | 5 | 10 | 6 | 7 | 17 | **82** |
| Caregivers | 5 | 2 | 4 | 1 | 0 | 3 | **15** |
| **TOTAL** | 47 | 8 | 14 | 7 | 7 | 20 | **103** |

## Table 5: Gender and Age of Survey Respondents

| Respondents | Age Range | | | | | Gender | | |
|---|---|---|---|---|---|---|---|---|
| | < 20 | 20-39 | 40-59 | ≥ 60 | Did not answer | Female | Male | Did not answer |
| Patients with BV + AVD experience | 0 | 3 | 3 | 0 | 0 | 3 | 3 | 0 |
| Patients without BV + AVD experience | 2 | 32 | 18 | 9 | 21 | 43 | 18 | 21 |
| Caregivers | 0 | 2 | 7 | 3 | 3 | 9 | 3 | 3 |
| Total | **2** | **37** | **28** | **12** | **24** | **55** | **24** | **24** |

From the patient's perspective, HL has a considerable physical, emotional and financial burden on the lives of patients. 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 significantly impacted patients' quality of life. When asked which aspect of their daily life was the most impacted by HL, the majority of patients stated that HL had greatly impacted their ability to work. The most common therapies for HL used by patients were ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine), radiation therapy, and autologous stem cell transplant. 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. Caregivers of HL patients also expressed financial and emotional challenges. More than half of the caregiver respondents (67%) stated that their caregiving duties had affected their ability to concentrate, contribute financially to the household, travel, and complete household chores. Six patients reported having experience with BV + AVD. The most common side-effects of BV + 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 quality of life; however, when asked to what extent they are willing to tolerate the side effects of BV + AVD, on a scale of 1-5 (1 = will not tolerate side effects; 5 = will tolerate significant side effects) 5 out of the 6 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 + 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. However, more than half of the patients (55%) stated that they would be willing to take a drug with known and potentially serious side-effects in favour of a cure or longer remission of the disease.

Of note, quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that are reported have also been reproduced as is according to the submission, without modification. Please see below for a summary of specific input received from the patient groups.

## 3.1 Condition and Current Therapy Information

### 3.1.1 Patients Experiences

LC asked respondents if they were a teenager or young adult (13-39 years old) at the time of diagnosis. Sixty-four patient respondents (74%) out of the 87 who responded reported that they were diagnosed with HL when they were a teenager or young adult; one patient chose not to answer. A total of 81 respondents provided a response when asked to recall what symptoms of HL had impacted their quality of life at the time of diagnosis. The most common symptoms reported were fatigue or lack of energy (58/81; 72%), enlarged lymph nodes (54/81; 67%), drenching night sweats (35/81; 43%), itching (34/81; 42%), and persistent cough (32/81; 40%). Symptoms reported by greater than 10% of the 81 patient respondents were unexplained weight loss, loss of appetite, trouble breathing, fever, chills, and chest pain.

Respondents were asked to report which aspects of their lives have been affected by HL. According to LC, the majority of the respondents (61%) reported that HL had a negative impact on their ability to work. The responses are summarized in Table 6.

### Table 6: Effect of HL on day-to-day life of patients

| Effect of HL on day-to-day life of patients (Total responses = 82) | |
|---|---|
| **Aspect of life NEGATIVELY impacted by HL** | **# of respondents** |
| Ability to work | 50 (61%) |
| Personal Image | 39 (47%) |
| Family obligations | 38 (46%) |
| Intimate relations | 30 (37%) |
| Friendships | 30 (37%) |
| Ability to attend school | 13 (16%) |
| None of these | 11 (13%) |

Respondents were also asked to indicate which challenges of living with HL had the greatest impact on their quality of life. The results are summarized in Table 7. As noted, anxiety/worry was the most common symptom/problem related to HL reported.

### Table 7: Effect of HL on current quality of life of patients

| Effect of HL on current quality of life of patients (Total responses = 82) | |
|---|---|
| **Symptom or problem related to HL** | **# of respondents** |
| Anxiety/worry | 38 (46%) |
| Problems concentrating | 28 (34%) |
| Loss of sexual desire | 27 (33%) |
| Stress of diagnosis | 24 (29%) |
| Difficulty sleeping | 24 (29%) |
| Memory loss | 24 (29%) |

| Effect of HL on current quality of life of patients (Total responses = 82) | |
|---|---|
| **Symptom or problem related to HL** | **# of respondents** |
| Depression | 20 (24%) |
| None of these | 8 (10%) |

The following are some comments provided by patients regarding their quality of life:

*"I experience more fatigue than I used to and although I'm able to work, I'm exhausted at the end of the day. Exercise is difficult to do on a weekday."* Female, 21-39, USA

*"I immediately lost my job, as I worked in an environment not safe for someone with a compromised immune system. I had to give up my study at uni, and both devastated me. I was very fit, but now if I try to exercise at the same level I become exhausted very easily. It's very hard."* Female, 21-39, Australia

*"I almost feel like I suffer from ptsd from this experience. I went into remission for about a year and then had a recurrence. I'm always worried it might come back. If I smell alcohol swabs - like they use before taking blood or administering chemo - my mind goes right back to treatment days - and that's more than 25 years ago."* Female, 50-59, Canada

### 3.1.2 Patients' Experiences with Current Therapy

All patient respondents reported that they had previously received treatment for HL or were currently receiving treatment. A total of 73 patient respondents provided information about their treatments, 68 of whom (93%) reported that they have been treated with at least one line of conventional chemotherapy. Twenty-eight (38%) patients reported that they had received two or more lines of chemotherapy and 12 (16%) had received three of more lines of chemotherapy. Table 8 lists all the treatments reported by patients. ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine), was the most common treatment used by patients (59/73; 81%), followed by radiation therapy (37/73; 51%).

## Table 8: Treatments used by Patients

| Treatments used by patients (Total responses = 73) | |
|---|---|
| **Treatments** | **# of respondents** |
| ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) | 59 (81%) |
| Radiation therapy | 37 (51%) |
| Autologous stem cell transplant | 19 (26%) |
| GDP (gemcitabine, dexamethasone, cisplatin) | 7 (10%) |
| Surgery | 7 (10%) |
| BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) | 6 (8%) |
| MOPP/COPP (mechlorethamine/cyclophosphamide, vincristine, procarbazine, prednisone) | 4 (5%) |
| Allogeneic stem cell transplant | 3 (4%) |
| Nivolumab | 1 (1%) |
| CAR-T therapy | 1 (1%) |

Seventy-six respondents indicated the phase of treatment that they are currently in, 50 (66%) of whom reported that they are in remission following their most recent line of therapy. Twenty-three (30%) have been in remission for longer than five years and 11 (15%) respondents had previously relapsed after one or more lines of therapy. On a 10-point scale (10=strongly agree), the respondents were asked how much they agree with the following statement: "My most recent therapy could manage my Hodgkin lymphoma symptoms." Fifty-five (72%) respondents gave a rating of ≥7. LC commented that this rating indicates that the most recent treatment for these patients was able to manage most of their HL symptoms.

Table 9 lists the side-effects of current HL treatments reported by patients. As noted, the most common side-effects reported by patients were fatigue (70/74; 95%), hair loss (67/74; 91%), and nausea/vomiting (65/74; 88%).

## Table 9: Side-effects of Current HL Therapies

| Side effects of current HL therapies (Total responses = 74) | | | |
|---|---|---|---|
| **Side effect** | **Responses** | **Side effect** | **Responses** |
| Fatigue | 70 (95%) | Loss of menstrual periods | 26 (35%) |
| Hair loss | 67 (91%) | Breathing difficulties | 23 (31%) |
| Nausea/vomiting | 65 (88%) | Infections | 23 (31%) |
| Mouth sores | 51 (69%) | Back pain | 22 (30%) |
| Peripheral neuropathy | 39 (53%) | Cough | 20 (27%) |
| Low platelets | 36 (49%) | Irregular heartbeat | 15 (20%) |
| Anemia and/or neutropenia | 34 (46%) | Bowel obstruction | 12 (16%) |
| Diarrhea | 33 (45%) | Viral reactivation (e.g. shingles) | 9 (12%) |
| Skin rashes/severe itching | 29 (39%) | | |

Fifty respondents provided a response about their ability to tolerate treatment-related side effects. Twenty-five respondents (50%) reported that nausea/vomiting were the most difficult side effects to tolerate followed by fatigue (23; 46%) and hair loss (11; 22%). Sixty-six respondents also reported that they had experienced one or more late or long-term treatment-related side effects (lasting longer than 2 years or appearing later than 2 years after the end of treatment), the most common of which were fatigue (43; 65%), “chemo-brain” (39; 59%), peripheral neuropathy (21; 32%), loss of menstrual periods (15; 23%), thyroid dysfunction (12; 18%), sterility (10; 15%), and lung damage (9; 14%).

Respondents were asked to report how their treatment experience impacted their quality of life (Table 10). Notably, treatment-related fatigue was the most common challenge significantly impacting patients’ quality of life as reported by 59 of the 74 (80%) patient respondents, followed by ability to tolerate treatments (44, 59%), number of clinic visits (43; 59%), infusion time (40; 54%), and infusion reaction (39; 53%) .

## Table 10: Negative Impact of Specific Aspects of Treatment

| Negative impact of specific aspects of treatment (Total responses = 74) | | | | |
|---|---|---|---|---|
| **Aspect of treatment** | **Weighted average** | **Rating = 7-10 (significant impact)** | **Rating = Not applicable** | **Total number of responses** |
| Treatment-related fatigue | 7.5 | 59 (80%) | 0 (0%) | 74 |
| Ability to tolerate treatment | 6.6 | 44 (59%) | (0%) | 74 |
| Infusion reaction | 6.3 | 39 (53%) | 6 (9%) | 71 |
| Infusion time | 6.3 | 40 (54%) | 5 (7%) | 74 |
| Number of clinic visits | 6.2 | 43 (58%) | 0 (0%) | 73 |
| Number of infections | 4.3 | 16 (22%) | 7 (10%) | 73 |
| Frequency of infections | 4.0 | 11 (15%) | 8 (11%) | 74 |

Respondents were asked to rate the negative effect of previous treatments on specific aspects of their daily lives (Table 11). The most common aspects of life reported to significantly impact the quality of life of patients were the ability to attend school (weighted average=8.86), ability to work (weighted average= 7.89), travel (weighted average=7.47), and activities (weighted average = 7.35).

## Table 11: Negative Impact of Previous Treatments on Quality of Life

| Negative impact of previous treatments on quality of life | | | | |
|---|---|---|---|---|
| **Aspect of life** | **Weighted average** | **Rating = 7-10 (significant impact)** | **Rating = Not applicable** | **Total number of responses** |
| Ability to attend school | 8.86 | 18 (24%) | 49 (66%) | 74 |
| Ability to work | 7.89 | 51 (69%) | 10 (14%) | 74 |
| Travel | 7.47 | 55 (75%) | 5 (7%) | 73 |
| Activities | 7.35 | 56 (76%) | 1 (1%) | 74 |
| Intimate relations | 7.08 | 48 (68%) | 4 (5%) | 71 |
| Family obligations | 6.14 | 41 (55%) | 2 (3%) | 74 |
| Friendships | 5.76 | 40 (54%) | 0 (0%) | 74 |

The following are some comments provided by patients, describing the impact of treatments on their quality of life.

*"The chemotherapy I received before and with my bone marrow transplant put me into premature menopause (i'm in my 20s) and that has negatively affected my intimate relations."* Female, 21-39, USA

*"My short term memory from chemo is very bad on some days, which effects me at work and home. I'm constantly tired, I work full time and have 4 children. One of whom I was pregnant with when diagnosed."* Female, 21-39, UK

*"I was unable to finish the first semester of nursing school at the time. I was unable to help coach basketball because of low self esteem from hair loss and fatigue. Did not really want to go places and visit friends because of hair loss."* Female, under 20, USA

Lymphoma Canada also asked respondents about their ability to access HL treatments. Fifty-five of the 74 respondents (79%) who responded reported that they were able to access treatments in their own community. Fifteen respondents (20%) reported that they were unable to access treatment in their own community; 11 of these respondents (73%) reported that that they lived in a community without a cancer centre, three (20%) reported that treatment was not available in their province, and one respondent reported that treatment was not available in their country. When asked about the financial burden of treatments, 48 out of the 70 respondents (69%) who responded reported that absence from work or school had a significant impact on their financial wellbeing. Other causes of financial difficulty reported by respondents included parking expenses (28; 40%), travel to and from appointments (20; 29%), and cost of medications (21; 30%).

### 3.1.3 Impact on Caregivers

Caregivers also expressed challenges regarding their caregiving experience. On a scale of 1 to 10 (1= no effect on quality of life; 10= significant negative effect), caregivers were asked to rate how their caregiving duties have impacted their daily activities and quality of life (Table 12). More than half of caregivers responded that their caregiving duties had significantly impacted their ability to concentrate (10; 67%), contribute financially to the household (9; 60%), travel (9; 60%), complete household chores (8; 53%), and volunteer (8; 53%).

## Table 12: Effect of Caregiving on Quality of Life

| Effects of caregiving on quality of life (Total responses = 15) | |
|---|---|
| **Daily activity** | **# of respondents who rated ≥ 7** |
| Ability to concentrate | 10 (67%) |
| Contribute financially to household | 9 (60%) |
| Travel | 9 (60%) |
| Attend to household chores | 8 (53%) |
| Volunteer | 8 (53%) |

| Effects of caregiving on quality of life (Total responses = 15) | |
|---|---|
| **Daily activity** | **# of respondents who rated ≥ 7** |
| Spend time with family and friends | 7 (47%) |
| Exercise | 5 (33%) |
| Fulfill family obligations | 4 (27%) |

The following are some comments provided by caregivers describing the impact of caregiving on their daily lives:

*"My 20 year old son was diagnosed with hl. This last year has been a nightmare. Family, friends don't call or even know what to say. We are left alone, while everyone's life continues."* Female, 40-59, USA

*"I was pregnant with twins while caring for my man and we did what we had to do and we stuck together. It was hard to be away from our older kids when he was receiving treatments but nurses in oncology dept. are angels."* Female, 20-39

*"I've become a caregiver. Scheduling my daughters appointments, managing her medicine. Taken over her care. She was in between jobs at diagnosis and her prospects for a new job has significantly decreased. We support her financially now."* Female, over 60, Canada

## 3.2 Information about the Drug Being Reviewed

### 3.2.1 Patient Expectations for New Therapies

Lymphoma Canada commented that patients value treatment options that will help control the disease and result in remission of the cancer. Ideally, patients would like these treatments to be associated with fewer side effects. On a scale of 1-10 (1 = not important; 10 = very important), respondents were asked to indicate how important it is for them and their physician to have the ability to choose which treatments to take. The majority of respondents (70/80, 88%) responded with a rating of 7,8,9 or 10, with a weighted average of 8.7. Respondents were also asked to indicate the most important outcome they expect from a new drug or treatment for HL, the majority of respondents (31/44; 70%) reported "effectiveness". Lymphoma Canada noted that although more than half of patients (25; 57%) also reported "minimal side effects" or "less side effects than current treatments" as very important, 55% of respondents also reported that they would be willing to take a drug with known and potentially serious side effects, if their doctor advised that it was the best choice for them.

### 3.2.2 Patient Experiences to Date

Six patient respondents reported having experience with BV + AVD as a first line treatment for HL. Five of these patients reported that they had received treatment more than two years ago and completed the full course of the treatment. Table 13 lists the characteristics of these patients, as well as their mode of access to the drug. Five out of the six patients were from Canada, three of whom accessed the drug through clinical trial. There was an equal proportion of males and females and all six patients were below the age of 60. The majority of patients (5/6) accessed the drug more than two years ago.

## Table 13: HL Patients with BV + AVD Experience

| HL patients with BV + AVD experience | | | | | |
|---|---|---|---|---|---|
| **Patient** | **Gender** | **Age** | **Location** | **BV treatment** | **Access to BV** |
| 1 | Male | 50-59 | USA | > 2 years ago | Public drug plan |
| 2 | Female | 40-49 | Canada | 1-2 years ago | Private insurance |
| 3 | Male | 20-29 | Canada | > 2 years ago | Clinical trial |
| 4 | Female | 40-49 | Canada | > 2 years ago | Clinical trial |
| 5 | Male | 20-29 | Canada | > 2 years ago | Paid out-of-pocket |
| 6 | Female | 30-39 | Canada | > 2 years ago | Clinical trial |

The six respondents were asked to indicate which symptoms were improved by the BV + AVD treatment (Table 14). The most common improved symptom, reported by all six patients was enlarged lymph nodes, followed by night sweats (3; 50%) and shortness of breath (3; 50%).

## Table 14: Resolution of Disease Symptoms with BV + AVD Treatment

| Resolution of disease symptoms with BV + AVD treatment | |
|---|---|
| **Disease symptom** | **# of respondents (N = 6)** |
| Enlarged lymph nodes | 6 (100%) |
| Night sweats | 3 (50%) |
| Shortness of breath | 3 (50%) |
| Pain | 2 (33%) |
| Fatigue, lack of energy | 1 (17%) |
| Fever | 1 (17%) |

Table 15 lists the side-effects of BV + AVD reported by respondents, the most common of which were peripheral neuropathy (6; 100%), neutropenia (5; 83%), fatigue (5, 83%), and nausea /vomiting (4; 67%).

## Table 15: Side-effects Experienced with BV + AVD

| Side effects experienced with BV + AVD (Total responses = 6) | | | |
|---|---|---|---|
| **Side effect** | **Number of responses** | **Side effect** | **Number of responses** |
| Peripheral neuropathy | 6 (100%) | Diarrhea | 2 (33%) |
| Neutropenia | 5 (83%) | Fever | 2 (33%) |
| Fatigue | 5 (83%) | Lung problems | 2 (33%) |
| Nausea/vomiting | 4 (67%) | Cough | 2 (33%) |
| Infections | 3 (50%) | Muscle or joint pain | 2 (33%) |
| Headache | 3 (50%) | Rash | 1 (17%) |
| Shortness of breath | 3 (50%) | Constipation | 1 (17%) |
| Infusion reaction | 3 (50%) | | |

On a scale of 1 - 4, (1 = no impact; 4 = very significant impact), respondents were asked to what extent, different aspects of BV + AVD therapy impacted their quality of life (Table 16). Side-effects of treatment was reported to have the most impact on the quality of life of patients (weighted average=2.8).

## Table 16: Impact of BV + AVID on Quality of Life

| Impact of BV + AVD on quality of life (Total responses = 6) | | | | | | |
|---|---|---|---|---|---|---|
| **Aspect of treatment** | **No impact (1)** | **Some impact (2)** | **Significant impact (3)** | **Very significant impact (4)** | | **Weighted average** |
| Number of clinic visits | 0 (0%) | 4 (67%) | 1 (17%) | 1 (17%) | 0 (0%) | 2.5 |
| Infusion time | 0 (0%) | 4 (67%) | 2 (33%) | 0 (0%) | 0 (0%) | 2.3 |
| Infusion reaction | 2 (33%) | 2 (33%) | 0 (0%) | 1 (17%) | 1 (17%) | 2.0 |
| Number or frequency of infections | 1 (17%) | 3 (50%) | 1 (17%) | 0 (0%) | 1 (17%) | 2.0 |
| Other side effects of treatment | 0 (0%) | 2 (33%) | 3 (50%) | 1 (17%) | 0 (0%) | 2.8 |

On a scale of 1-5 (1 = will not tolerate side effects; 5 = will tolerate significant side effects), respondents were asked to indicate to what extent they are willing to tolerate the side effects of BV + AVD. The majority of patients (5/6) provided a rating of 4 or higher, indicating that many patients are willing to tolerate significant side-effects in favour of a cure or longer remission of the cancer.

The following are some comments provided by patients regarding their experience:

*"While the side effects were harsh and long lasting, the treatment saved my life."*

*"Side effects were really tough, but it worked and I'm feeling close to 100% almost 2 years after treatment."*

*"It was a successful front line defense to an aggressive and life-threatening HL lymphoma diagnosis (stage 4B)."*

All six respondents responded that they would be willing to take the treatment again if their doctor recommended that it was the best treatment option for them.

Respondents were asked to indicate on a 5-point scale (1 = Much worse off; 5 = Greatly improved), how BV + AVD had influenced different aspects of their lives (Table 17). The majority of respondents responded that the drug had a positive or no impact on their ability to work (weighted average =3.4), attend school (weighted average = 3.3); fulfill family obligations (weighted average =3.3), and perform household chores (weighted average = 3.3).

## Table 17: Impact of BV + AVD on Activities of Daily Living

| Impact of BV + AVD on Activities of Daily Living (Total responses = 6) | | | | | |
|---|---|---|---|---|---|
| **Aspect of daily living** | **Worse off (score = 1-2)** | **Unchanged (score = 3)** | **Improved (score = 4-5)** | **Not Applicable** | **Weighted Average** |
| Ability to work | 1 (17%) | 2 (33%) | 2 (33%) | 1 (17%) | 3.4 |
| Ability to fulfill family obligations | 1 (17%) | 3 (50%) | 2 (33%) | 0 (0%) | 3.3 |
| Ability to perform household chores | 1 (17%) | 3 (50%) | 2 (33%) | 0 (0%) | 3.3 |
| Ability to attend school | 1 (17%) | 1 (17%) | 2 (33%) | 2 (33%) | 3.3 |
| Ability to exercise | 2 (33%) | 2 (33%) | 2 (33%) | 0 (0%) | 3.2 |
| Ability to contribute to household finances | 1 (17%) | 2 (33%) | 1 (17%) | 2 (33%) | 3.0 |
| Ability to volunteer | 1 (17%) | 1 (17%) | 1 (17%) | 3 (50%) | 3.0 |

Respondents were asked to indicate how the treatment with BV + AVD has changed their health and wellbeing (Table 18). Overall, all six respondents noted that the drug has somewhat or greatly improved their health and wellbeing.

## Table 18: Impact of BV + AVD on Health and Wellbeing

| Impact of BV + AVD on health and wellbeing (Total responses = 6) | | | | | |
|---|---|---|---|---|---|
| **Much worse off (1)** | **Somewhat worse off (2)** | **Unchanged (3)** | **Somewhat improved (4)** | **Greatly improved (5)** | **Weighted Average** |
| 0 (0%) | 0 (0%) | 0 (0%) | 2 (33%) | 4 (67%) | 4.7 |

Respondents were also to rate their overall experience with the drug. Overall, all six respondents reported that their experience with BV + AVD was positive (good, very good, or excellent) (Table 19).

## Table 19: Overall Experience with BV + AVD

| Overall experience with BV + AVD (Total responses = 6) | | | | | |
|---|---|---|---|---|---|
| **Poor (1)** | **Satisfactory (2)** | **Good (3)** | **Very good (4)** | **Excellent (5)** | **Weighted Average** |
| 0 (0%) | 0 (0%) | 2 (33%) | 3 (50%) | 1 (17%) | 3.8 |

## 3.3 Companion Diagnostic Testing

Not applicable

## 3.4 Additional Information

Not applicable

# 4 Summary of Provincial Advisory Group (PAG) Input

The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.cadth.ca/pcodr). PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

**Overall Summary**

Input was obtained from **all nine** provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- Use with other front-line combination chemotherapy
- Sequencing of other therapies downstream
- Re-treatment practicalities downstream

Economic factors:

- Potential for drug wastage
- Additional nursing and clinic resources will be required

Please see below for more details.

## 4.1 Currently Funded Treatments

PAG noted that the current standard frontline treatment for Hodgkin's lymphoma (HL) is doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD). An alternative regimen for young and healthy patients for whom the infertility implications are acceptable is BEACOPP (bleomycin/etoposide/doxorubicin/cyclophosphamide/vincristine/procarbazine /prednisone) which can be given in fixed or escalated doses. In some provinces, CVPP (cyclophosphamide, vinblastine, procarbazine, and prednisone) can be given to patients with contraindications to anthracyclines and/or bleomycin.

PAG noted that the ECHELON-1 trial compared brentuximab vedotin (BV) combined with AVD to ABVD, which is the main standard of care in Canada and thus a relevant comparator.

## 4.2 Eligible Patient Population

The reimbursement request is for the treatment of previously untreated patients with Stage IV Hodgkin lymphoma (HL) in combination with doxorubicin, vinblastine, and dacarbazine (AVD). In view of on the characteristics of the patient population in the ECHELON-1 trial, PAG is seeking clarity on whether the following patients would be eligible for treatment with BV:

- Patients less than 18 years of age
- Patients with an ECOG performance score greater than 2
- Patients with stage III HL (included in the trial) and stage IIB
- Nodular lymphocyte-predominant HL
- Patients with cardiovascular conditions
- 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. 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. In addition, PAG noted a potential for indication creep with BV for patients with earlier stages of disease and in other lines of therapy. There is also the potential of combining BV with chemotherapies other than AVD. Regarding the latter, PAG is seeking guidance on potentially substituting etoposide for patients unable to receive doxorubicin.

## 4.3 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.

PAG noted that drug wastage is a significant barrier as only 50 mg vials are available and patients may require up to three vials (120 mg = 1.2 mg/kg IV for a 100 kg patient) per treatment cycle. Furthermore, the drug has 24 hours of stability after reconstitution and vial sharing may be challenging. PAG identified that the 30-minute infusion is an enabler to implementation.

Additional resources (e.g., nursing and clinic visits) are required to monitor and treat infusion-related reactions and adverse events (e.g. diarrhea, neutropenia/febrile neutropenia, and peripheral neuropathy) as well as monitor complete blood count. PAG noted that the rates of neutropenia are higher with BV + AVD compared with ABVD treatment. 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.

BV is already used for HL after ASCT and for other indications; health care professionals are familiar with its preparation, administration and monitoring for adverse events. However, PAG noted the potentially significant budget impact from moving this costly biologic therapy to the front line. Being an intravenous drug, BV would be administered in an outpatient chemotherapy center for appropriate administration and monitoring of infusion related reactions. Intravenous chemotherapy drugs would be funded fully in all jurisdictions for eligible patients which is an enabler. However, in some areas, patients would need to travel far to an outpatient chemotherapy center, which would be a barrier to for these patients.

## 4.4 Sequencing and Priority of Treatments

PAG is seeking to confirm the eligible patient population and line of therapy with BV, and the possible sequencing of treatments, including the scenarios below:

- Situations where preference would be given to BV + AVD vs ABVD and BEACOPP.
- Options after progression with BV including allogeneic stem cell transplant and immunotherapies. In this situation, PAG also seeks guidance on potential re-treatment with BV upon relapse.
- Combination of BV with other first line chemotherapies such as BEACOPP. Could BV also replace bleomycin in the latter?
- Evidence for continuing brentuximab as a single agent for high risk patients after completion of BV + AVD.

## 4.5 Companion Diagnostic Testing

CD30 testing is routinely done in pathology labs across Canada and would not represent an additional burden.

## 4.6 Additional Information

None.

# 5 Summary of Registered Clinician Input

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) for the review of Brentuximab Vedotin (Adcetris) for the treatment of previously untreated patients with Stage IV HL, in combination with AVD. Current treatments identified by clinicians for Stage IV Hodgkin Lymphoma were ABVD and BEACOPP. Both clinician inputs stated that the patient population in the reimbursement request aligns with the need in clinical practice. The clinician from CCO, however, recommends greater flexibility with blood counts as low blood counts are most likely due to the disease and could potentially improve with treatment. The clinicians from LC stated that although Stage III and Stage IV patients are treated similarly as those in the ECHELON-1 trial, the current Health Canada approval is for Stage IV patients only. BV + AVD may be a good option for some subgroups of patients such as those over 60 or those with comorbidities, for whom the use of BEACOPP and AVD may be limited due to toxicity issues. For the subgroup of patients who are below the age of 18, the clinician from CCO noted that currently there is a lack of evidence directing the use of BV + AVD, whereas the clinicians from LC noted that the drug may be used because of similar disease biology. The clinicians from LC explained that BV + 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 + AVD would most likely be used as a complementary treatment, since there are multiple front-line options available. Patients who are ineligible for BEACOPP are a definitive subgroup of patients that would benefit from BV + AVD. Both clinician inputs noted that neutropenia and peripheral neuropathy may be potential side effects of BV + AVD, in which case, patients would likely receive G-CSF with BV + AVD. The clinicians from LC further commented that patients with pre-existing neuropathy would be unlikely to receive BV + AVD and would also likely have challenges with AVD and BEACOPP. As BV + 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 + AVD treatment would unlikely receive BV-based treatments; however, BV can be considered for patients that did not experience significant toxicity after relapsing on BV + AVD. The clinician from LC prefers the use of BV + 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, BEACOPP will be used less compared to BV + AVD.

## 5.1 Current Treatment(s)

Both groups of clinicians agreed that the current treatments for the indication under review are ABVD and BEACOPP. The joint clinician input further commented that most clinicians who treat advanced HL use the PET-adapted approach starting with ABVD, where PET imaging after two cycles of treatment is used to direct escalation (i.e., to BEACOPP) or de-escalation (i.e., to AVD) of therapy. Some patients may receive only ABVD without a risk adapted, PET-guided approach. A subset of patients may be treated initially with BEACOPP, then de-escalated to either ABVD or fewer cycles of ABVD.

## 5.2 Eligible Patient Population

The clinician from CCO agreed that the patient population in the reimbursement request aligns with the need in clinical practice. An improvement in first-line outcomes may lead to the reduced use of BEACOPP and also less use for second-line salvage therapy (GDB and auto-transplant). The clinician stated that the inclusion and exclusion criteria in the trial are applicable to clinical practice; however, the clinician recommends greater lenience with blood count requirements than those seen in the trial, as suboptimal counts are most likely due to the disease. Even if blood counts are low in the beginning, they could potentially improve with treatment. The clinicians from LC noted that Stage III and Stage IV patients are managed similarly as in the ECHELON-1 trial. However, the clinicians noted that Health Canada approval is only for patients with Stage IV disease, which is based on weaker evidence from a subset analysis. For some patient sub-groups such as those over 60 years of age or patients with comorbidities, the use of ABVD or BEACOPP may be limited due to toxicity issues. For these subgroups, the clinicians prefer to have BV + AVD as an option and use standard decision making to determine if the drug is acceptable.

### 5.2.1 Is there evidence or information to extrapolate use of BV+AVD in patients less than 18 years of age? What would be the age cut-off if there is a recommendation to use in patients less than 18 years of age?

The clinicians from LC noted that currently there is a lack of available data to inform the use of BV + AVD in patients less than 18 years of age. The clinician from CCO responded that the drug could potentially be used for this group of patients, since the biology of the disease is similar. Both groups of clinicians advised CADTH to consult pediatric lymphoma specialists.

## 5.3 Relevance to Clinical Practice

The clinician from CCO advised that this drug would be used as a standard first-line therapy, in which case BEACOPP would not be used as an initial therapy. The clinician stated that the drug is not associated with any significant toxicities; however, neutropenia may be a side effect, in which case a patient may require more G-CSF. The joint clinicians noted that BV + AVD has proven to be better than ABVD without PET-based modification of therapy. However, the clinicians believe that adopting BV + AVD might present some challenges as standards with PET-adapted protocols have changed since the ECHELON-1 trial. Since multiple frontline treatments are available, the clinicians expect that BV + AVD would be another complimentary treatment. Patients who are ineligible for BEACOPP would be a clear subgroup of patients who would benefit from BV + AVD. The clinicians also mentioned that in the case of febrile neutropenia and peripheral neuropathy, patients would likely receive G-CSF with BV + AVD. Patients with pre-existing neuropathy would be unlikely to receive BV + AVD, and would also likely have challenges with AVD and BEACOPP. Older patients would continue with radiation therapy as a treatment as IV chemotherapy would not be appropriate for them.

## 5.4 Sequencing and Priority of Treatments with New Drug Under Review

The individual clinician commented that if BV + AVD is funded, it might be commonly used. Being a first-line treatment, the clinicians from LC stated that there could be some consequences in further lines of treatments. BV is commonly used for patients who are receiving salvage therapy prior to ASCT, as maintenance for patients after ASCT, and as a palliative therapy for patients who have been heavily treated for the disease. For patients that are refractory to BV + AVD, there is currently no evidence that shows that BV is effective post-ASCT consolidation therapy or as monotherapy. The clinicians believe that this group of patients would unlikely receive subsequent BV-based treatments, due to the cost, toxicity profile, and the availability to alternative treatments. If funded or if a trial is available, BV can be considered for patients that did not experience any significant toxicity after relapsing post BV + AVD.

### 5.4.1 What circumstances would drive the preference to prescribe BV+AVD vs ABVD or BEACOPP?

The clinician from CCO stated that they prefer to use BV + AVD as the main option. BEACOPP can be used as an initial therapy but due to its toxicity/fertility issues, it is more likely to be used in a PET-directed algorithm. The clinician believes that even in a PET-directed algorithm, upfront use of BEACOPP will probably be less compared to BV + AVD.

The clinicians from LC noted that data from three key RCTs (representing Germany, UK and France) use different standard approaches for the treatment of advanced HL. The German approach as outlined in the HD18 trial, used a PET-guided approach to determine if two cycles of standard regimen eBEACOPP (PET-2) would allow for the modification of treatment intensity - increasing eBEACOPP cycles for PET-2-positive patients and reducing the cycles for PET-2-negative patients. The French approach as outlined in the AHL 2011 trial investigated whether PET monitoring during treatment would allow dose de-escalation by switching regimens (BEACOPP escalation to ABVD) without loss of disease control compared with standard treatment without PET monitoring. The most commonly used approach in Canada is the UK (RATHL) approach. The typical standard is ABVD-based therapy and a subset of these patients will go onto BEACOPP. Clinicians are likely to use the following three approaches:

1. ABVD can be used initially followed by the RATHL algorithm.
2. BV + AVD will be used initially and will be continued in PET2 negative patients. A subset of patients may be escalated to BEACOPP or continued on BV + AVD as per the ECHELON-1 trial, especially if there are concerns about toxicity from BEACOPP.
3. BEACOPP will be used initially and then as per the French or German approach, have treatment adjusted by a risk adapted PET-guided approach. This would be a small subset of patients and will most likely be driven by adverse prognostic features at baseline.

The clinicians from LC emphasized that clinicians will continue to use treatments regimens that don't include BEACOPP or BV + AVD and that these commonly used options should remain funded as standard options.

### 5.4.2 Is there evidence to inform the effectiveness and timing of re-treatment with BV in patients who progress or relapse after downstream therapies?

The clinician from CCO believes that BV can be used by patients again if there is sensitivity to it upfront.

The clinicians from LC noted that currently there is unclear evidence to inform the effectiveness and timing of re-treatment with BV in patients who progress or relapse after downstream therapies. There are small, published studies of re-treatments in patients who

have received prior BV, that show similar response rates to monotherapy with BV. The clinicians emphasized that timing of re-treatment, along with persistent drug-related toxicity are the most common factors that clinicians would use to determine whether patients should be re-treated with BV.

## 5.5 Companion Diagnostic Testing

The clinicians from LC acknowledged that it is very uncommon for HL biopsies to not express CD30.

## 5.6 Implementation Questions

**5.6.1 In your practice, what indicator is used to confirm disease progression? What imaging is used and how often are patients scanned during and after treatment?**

The clinicians from LC noted that symptoms or physical examinations are commonly used to identify disease progression. Imaging and biopsies can confirm the progression of the disease. After treatment is complete, follow-up imaging tests are not recommended and not commonly practiced in Canada. Clinicians may however advise 1-2 imaging scans in the first 3-12 months after full completion of therapy.

The clinician from CCO stated that typically, patients are scanned mid-course of treatment or after two cycles, and at the end of therapy. Standard imaging requirements using CT or PET/CT are used to confirm disease progression or relapse.

**5.6.2 If BV+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?**

The clinician from CCO recommends that patients should receive primary prophylaxis with G-CSF with BV + AVD. Depending on neutrophil counts, the number of days of G-CSF can be reduced to a minimum.

Clinicians from LC noted that based on a review of current data, the FDA has recommended a blanket approach to febrile neutropenia prophylaxis with BV + AVD. Age is a key risk factor of febrile neutropenia, as demonstrated in the ECHELON-1 trial. The clinicians asserted that it might be reasonable to restrict G-CSF primary prophylaxis to patients over the age of 60 or patients with comorbidities that can lead to infections. The clinicians further commented that it is now more common to treat HL patients with ABVD in Canada, without any delay or dose reductions in patients with neutropenia (ANC < 1.0 and lower) without G-CSF. Delay or dose reductions can affect patient outcomes and therefore G-CSF should be allowed in this patient population, which would be similar to the approach with R-CHOP in the curative setting.

## 5.7 Additional Information

Not applicable.

# 6 Systematic Review

## 6.1 Objectives

The primary objective of this review is to evaluate the efficacy and safety of brentuximab vedotin (Adcetris), in combination with doxorubicin, vinblastine, and dacarbazine (AVD), compared to standard of care in Canada for previously untreated patients with Stage IV Hodgkin lymphoma (HL).

## 6.2 Methods

### 6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the CGP and the CADTH Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below (Table 20). Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold. The literature search strategy and detailed methodology used by the CADTH Methods Team are provided in Appendix A.

### Table 20: Selection Criteria

| Clinical Trial Design | Patient Population | Intervention | Appropriate Comparators* | Outcomes |
|---|---|---|---|---|
| Published or unpublished RCTs.<br><br>In the absence of RCT data, fully published clinical trials investigating the efficacy and safety of BV + AVD should be included. | Patients with previously untreated advanced classic HL<br><br>Subgroups<br>• Age<br>  ○ <18 vs. ≥18<br>  ○ <60 vs. ≥60<br>• Clinical stage at diagnosis<br>  ○ IIb, III, IV<br>• ECOG PS<br>• IPFP Score<br>• Region<br>  ○ North America | BV + AVD<br>x 6 cycles | Not PET-guided<br>• ABVD x 6 cycles ± RT<br><br>PET-guided<br>• ABVD x 2 cycles + PET-response adapted treatment | Efficacy<br>• **PFS (or mPFS)**<br>• **OS**<br>• **CR**<br>• **HRQoL**<br><br>Safety<br>• **AEs**<br>  ○ Neutropenia<br>  ○ Peripheral neuropathy<br>  ○ Pulmonary toxicity |

*ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine; AE = adverse event; BV + AVD = brentuximab vedotin plus doxorubicin, vinblastine, dacarbazine; CR = complete remission; ECOG PS = Eastern Cooperative Oncology Group performance status; HL = Hodgkin lymphoma; HRQoL = health-related quality of life; OS = overall survival; IPFP = International Prognostic Factor Project; PFS = progression-free survival; RCTs = randomized controlled trial; RT = radiation therapy*

** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions) that are administered with curative intent. Although escalated BEACOPP regimens (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) may be an option for treatment of advanced cHL this combination is prescribed only to select patients (e.g., age < 60 years, ECOG 0-2, no major comorbidities), which constitutes a minority of the relevant patient population. Thus, due the limited use, escalated BEACOPP was not considered a relevant comparator for the purpose of this review.*

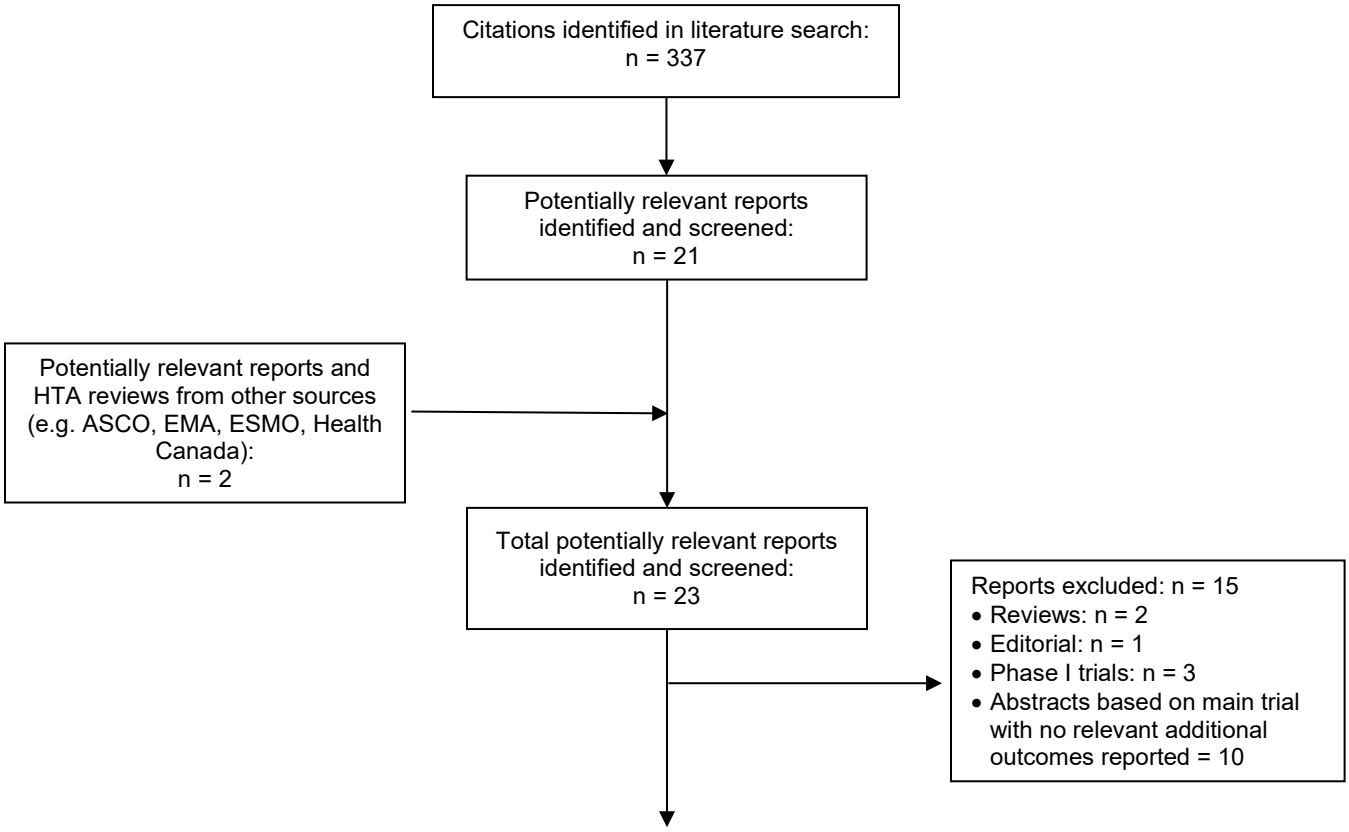
## 6.3 Results

### 6.3.1 Literature Search Results

Of the 337 potentially relevant reports identified, one unique study[2] was identified and included in this report, and 331 citations were excluded. Of those deemed potentially most relevant, citations were excluded because the trial design was not relevant to this review[31-33] (i.e., Phase I) or they were reviews[34,35] or editorial[36] in nature. Furthermore, although many abstracts reporting different

analyses from the ECHELON-1 study were identified, most were excluded as the outcomes were not relevant to this report.[37-46] Additionally, European Medicines Agency's Assessment Report and Health Canada's Reviewer's Report were included.

## Figure 1: Flow Diagram for Study Selection




| **7 citations and reports presenting data from 1 unique RCT included in this report** |
|---|
| **ECHELON-1 Study** |
| Connors et al., 2018[2] |
| Clinicaltrials.gov (ECHELON-1, NCT01712490 record)[47] |
| **Data Update or Subgroup Analysis, Full Publication** |
| Ramchandren et al., 2019 (North American population)[9] |
| Straus et al., 2020 (3-year update)[6] |
| **Data Update, Conference Abstract / Presentation** |
| Bartlett et al., 2019 (4-year update)[5] |
| **Reports identified from other sources** |
| Health Canada Reviewer's Report: Adcetris[48] |
| European Medicines Agency Assessment Report: Adcetris[4] |

*Note: Additional data related to the ECHELON-1study were also obtained through requests to the Sponsor by CADTH.[3,7,8,48,49]*

### 6.3.2 Summary of Included Studies

One randomized controlled trial that met the selection criteria of this review was identified.[2] ECHELON-1 is an ongoing, open-label, randomized, Phase III trial that compares brentuximab vedotin in combination with doxorubicin, vinblastine, dacarbazine (BV + AVD)

to the combination regimen of doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD) in patients with previously untreated advanced classic HL. Key characteristics of the ECHELON-1 trial are summarized in Table 21. Published follow-up data will also be discussed. Of note, since a Phase III trial was identified, studies of other clinical trial phases (e.g., Phase I or II) will not be summarized in this review.

#### 6.3.2.1 Detailed Trial Characteristics

## Table 21: Summary of Trial Characteristics of the Included Studies

| Trial Design | Inclusion Criteria | Intervention and Comparator | Trial Outcomes |
|---|---|---|---|
| **Study:**[2,47]<br>ECHELON-1<br>NCT01712490<br><br>**Characteristics:**<br>Phase III, open-label, randomized (1:1), active-controlled trial<br><br>N = 1334 randomized (664 = BV + AVD; 670 = ABVD)<br><br>Randomization stratified by:<br>• Region (Americas vs. Europe vs. Asia)<br>• Number of IPFP risk factors (0-1 vs. 2-3 vs. 4-7)<br><br>**Setting:**<br>218 sites in 21 countries (Canada, Australia, Belgium, Brazil, Czechia, Denmark, France, Hong Kong, Hungary, Italy, Japan, Korea, Norway, Poland, Russia, South Africa, Spain, | Key Inclusion Criteria:<br>• ≥ 18 years of age with Ann Arbor Stage III or IV histologically confirmed classic HL according to WHO classification*<br>• Treatment-naïve<br>• ECOG PS ≤ 2<br>• Bidimensional measurable diseases by radiographic technique (spiral CT preferred) according to IWG Revised Criteria for Response Assessment for Malignant Lymphoma<br>• Clinical laboratory values (ANC, PLT, total bilirubin, ALT or AST, SCr, Hg) meeting criteria within 7 days prior to first dose of study drug†<br>• Female patients: post-menopausal for ≥1 year prior to screening, surgically sterile, or agree to acceptable contraceptive methods; male patients: agree to acceptable contraceptive methods<br><br>Key Exclusion Criteria:<br>• Nodular lymphocyte predominant HL<br>• Cerebral or meningeal disease, including signs or symptoms of PML<br>• Neurologic disease requiring medication or compromising normal ADL<br>• Peripheral sensory or motor neuropathy<br>• Active infection within 2 weeks prior to first study drug dose<br>• Prior immunosuppressive chemotherapy, RT, or any immunotherapy within 12 weeks before first study drug dose | Intervention:<br>**BV + AVD**<br>Brentuximab vedotin 1.2 mg/kg IV<br>Doxorubicin 25 mg/m$^2$ IV<br>Vinblastine 6 mg/m$^2$ IV<br>Dacarbazine 375 mg/m$^2$ IV<br><br>Administered as infusions on Days 1 and 15 of each 28-day cycle.<br><br>Maximum of 6 cycles.<br><br>Comparator:<br>**ABVD**<br>Doxorubicin 25 mg/m$^2$ IV<br>Bleomycin 10 units/m$^2$ IV<br>Vinblastine 6 mg/m$^2$ IV<br>Dacarbazine 375 mg/m$^2$ IV<br><br>Administered as infusions on Days 1 and 15 of each 28-day cycle.<br><br>Maximum of 6 cycles. | Primary:<br>• mPFS§<br><br>Secondary:<br>*Key*<br>• OS<br>*Others*<br>• CR rate<br>• EFS<br>• DFS<br>• ORR<br>• DOR<br>• Cycle 2 PET negativity<br>• PROs (EORTC QLQ-C30)<br>• PK parameters<br>• Presence of ATA to brentuximab vedotin<br>• Safety (TEAEs, SAEs)<br><br>Exploratory:<br>• PROs (FACIT-Dyspnea 10, FACT/GOG-Ntx Abbreviated)<br>• HRQoL (EQ-5D-3L)<br>• % alive without HL (3 and 5 years)<br>• % switching therapy post Cycle 2 and pre-EOT<br>• Medical resource utilization<br>• Incidence of pregnancy<br>• PFS |

| Trial Design | Inclusion Criteria | Intervention and Comparator | Trial Outcomes |
|---|---|---|---|
| Taiwan, Tukey, United Kingdom, United States)<br><br>**Patient Enrolment Dates:**<br>November 19, 2012 to January 13, 2016<br><br>**Data cut-off:**<br>April 20, 2017<br><br>**Final Analysis Date:**<br>To be conducted after 112 deaths have occurred<br><br>**Funding:**<br>Millennium Pharmaceuticals Inc. and Seattle Genetics Inc. | • Known HIV or HBV positive, or active HCV infection<br>• Treatment or diagnosis of another malignancy within 3 years prior to first study drug dose, or have evidence of residual disease from previous malignancy‡<br>• Following CV conditions within 6 months prior to first study drug dose:<br>  ○ LVEF < 50%<br>  ○ MI within 2 years of randomization<br>  ○ NYHA Class III or IV HF<br>  ○ Uncontrolled CV conditions (e.g., cardiac arrhythmias, CHF, angina, acute ischemia or active conduction system abnormalities seen on ECG) | | |

*ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine; ADL = activities of daily living; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; ATA = antitherapeutic antibodies; BV + AVD = brentuximab vedotin plus doxorubicin, vinblastine, dacarbazine; CR = complete remission; CrCl = creatinine clearance; CHF = congestive heart failure; CR = complete remission; CV = cardiovascular; DFS = disease-free survival; DOR = duration of response; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EFS = event-free survival; EORTC = European Organisation for Research and Treatment of Cancer; EOT = end of treatment; FACT/GOG-Ntx Abbreviated = abbreviated Functional Assessment of Cancer Therapy/Gynecologic Oncology Group - Neurotoxicity; FACIT-Dyspnea 10 = Functional Assessment of Chronic Illness Therapy – Dyspnea 10-item short form questionnaire; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; Hg = hemoglobin; HL = Hodgkin lymphoma; HRQoL = health-related quality of life; IPFP = International Prognostic Factor Project; IWG = International Working Group; IV = intravenous; LVEF = left ventricular ejection fraction; MI = myocardial infarction; mPFS = modified progression-free survival; NYHA = New York Heart Association; ORR = objective response rate; OS = overall survival; PK = pharmacokinetic; PLT = platelet; PML = progressive multifocal leukoencephalopathy; PRO = patient-reported outcome; RT = radiation therapy; SCr = serum creatinine; SAE = serious adverse event; TEAE = treatment-emergent adverse event; WHO = World Health Organization*

* WHO classification includes nodular sclerosis, mixed cellularity, lymphocyte rich, lymphocyte depleted, or classical Hodgkin lymphoma not otherwise specified

† Specified clinical laboratory values include:

- ANC ≥ 1,500/µL and PLT count ≥ 75,000/µL unless known HL marrow involvement
- Total bilirubin < 1.5x upper limit of normal (ULN) unless due to Gilbert syndrome
- ALT or AST < 3x the ULN range. AST and ALT may be elevated up to 5x the ULN if reasonably ascribed to presence of HL in liver.
- SCr < 2.0 mg/dL and/or CrCl or calculated CrCl ≥ 40 mL/minute
- Hg ≥ 8 g/dL

‡ Nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they had been completely resected

§ mPFS, as measured by an independent review facility, was defined as time from date of randomization to the date that the first of the following occurred: 1) documentation of progressive disease; 2) death due to any cause; or 3) in confirmed noncomplete responders, receipt of anticancer chemotherapy or RT after completion of frontline treatment

### a) Trials

ECHELON-1 trial is an ongoing international, open-label, Phase III, randomized, active-controlled, superiority trial of brentuximab vedotin plus doxorubicin, vinblastine, dacarbazine (BV + AVD) versus doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD) in treatment-naïve patients with Stage III or IV classic Hodgkin lymphoma.[2] This study is being conducted at 218 sites in 21 countries, which are listed in Table 21, and includes 60 patients treated in Canada, representing the provinces of British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Quebec, and Nova Scotia.[3]

**Trial Design**

Screening and Randomization

Patients were recruited by investigators from their local practice or through referrals from other physicians and were screened within 4 weeks of randomization.[2] Key inclusion and exclusion criteria are outlined in Table 21. Briefly, patients were adults who had treatment-naïve 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, and those with sensory or motor peripheral neuropathy were excluded.

Eligible patients were randomized in a 1:1 ratio to receive open-label treatment with BV + AVD or ABVD. Randomization, performed within 24 hours of first dose, was stratified by region (Americas vs. Europe vs. Asia) and number of International Prognostic Factor Project (IPFP) risk factors (International Prognostic Score [IPS] 0-1 vs. 2-3 vs. 4-7).[2]

Treatment

Details of treatment regimens are outlined below under Section *c) Interventions*. Briefly, patients were randomized to receive one of two combination frontline treatments:

BV + AVD: brentuximab vedotin, doxorubicin, vinblastine, dacarbazine or

ABVD: doxorubicin, bleomycin, vinblastine, dacarbazine

Each agent was administered as an IV infusion on Days 1 and 15 of a 28-day cycle; treatment was continued up to a maximum of six cycles. Prior to completion of frontline therapy, switching to an alternative treatment regimen of physician's choice, guided by results from a PET scan (i.e., if PET scan showed a Deauville score of 5) taken after Cycle 2 Day 25, was permitted.[2]

Treatment may have been discontinued prior to six cycles if there was progressive disease, unsatisfactory therapeutic response, adverse event, protocol violation, withdrawal by subject, lost to follow-up, study termination by sponsor, or other reason.[2]

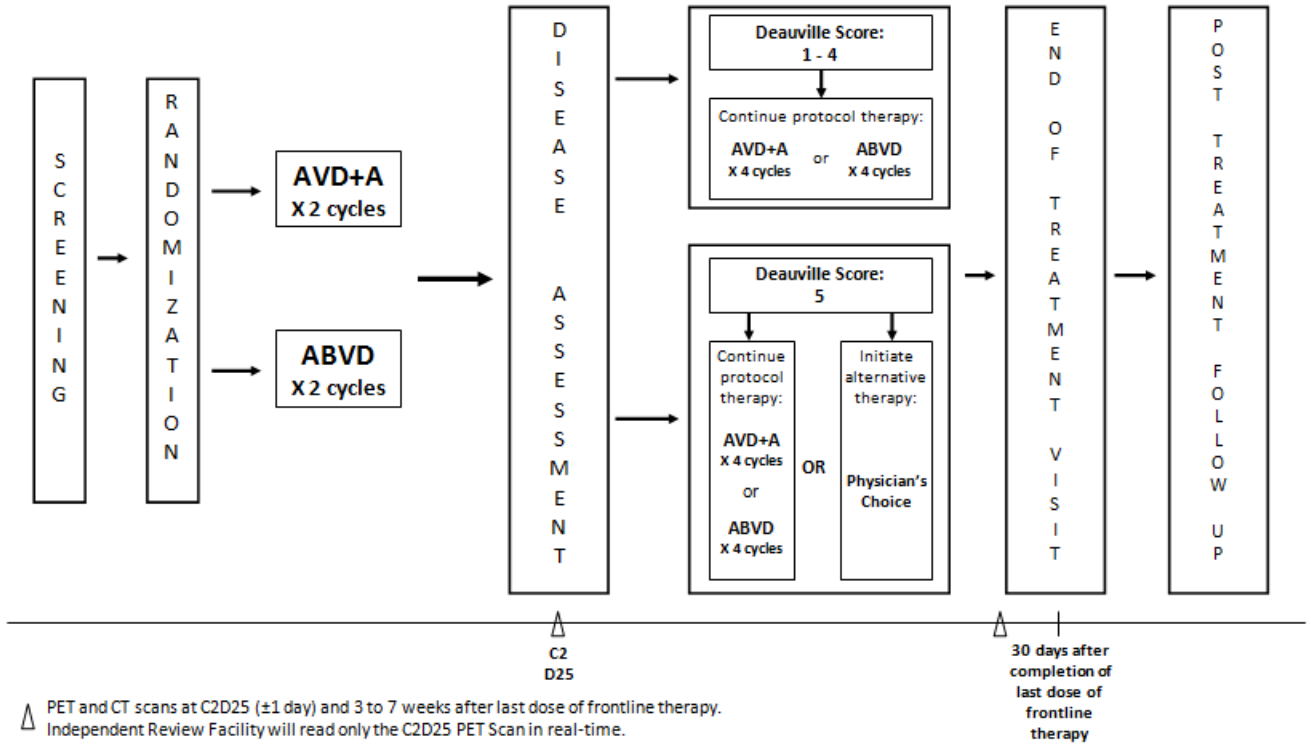
Monitoring and Disease Assessments

Patients were regularly monitored throughout treatment. In addition to disease status and safety, assessments of fertility, pharmacokinetic (PK)/ pharmacodynamic parameters, and immunogenicity were also routinely evaluated.[2]

During the treatment phase, tumour measurements via PET and CT scans of neck, chest, abdomen, and pelvis were performed at baseline, on Day 25 of treatment Cycle 2 (PET2), and at EOT. In patients who switched therapy prior to completion of randomly assigned treatment, PET and CT scans were required prior to starting the alternative regimen. CT scan results were used to help assess treatment response and disease status, according to the Revised Response Criteria for Malignant Lymphomas, and assessed by investigators as well as by an IRF that was blinded to treatment assignment. PET scans were also assessed by the blinded IRF using the Deauville criteria. The EOT disease assessment (CT and PET scans) was performed between 3 and 7 weeks following last dose of frontline therapy. An EOT visit was also scheduled for other assessments 30 ± 7 days after last dose of frontline therapy; thereafter, patients entered the post-treatment follow-up phase.[2]

Other specific disease assessments included a tumor biopsy during screening and at EOT, as well as B symptom assessment during screening, EOT, and Day 1 of each treatment cycle. An overview of the ECHELON-1 study design is shown in Figure 2.[2]

## Figure 2. Overview of ECHELON-1 Study Design




*Note: BV + AVD appears as AVD+A in the figure.*
Source: From the New England Journal of Medicine, Connors JM et al., Brentuximab vedotin with chemotherapy for stage III or IV Hodgkin's lymphoma, 378, 331-344. Copyright ©2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[2]

Follow-up

Regardless of the duration of treatment received, patients were followed after the last dose of study drug until consent withdrawal, lost to follow-up, study closure, or after being followed for 5 years (which was changed in post-publication protocol amendment to 10 years) from randomization.[2,3] Evaluations were performed until documented progressive disease, receipt of second-line treatment for HL, death, or end of study. Patients who discontinued study drug prior to completing the full six cycles for reasons other than progressive disease, were also followed for post-treatment assessments until disease progression, withdraw of consent, or initiation of another anticancer treatment (second-line therapy) for patients not in complete remission after frontline therapy.[2]

During the post-treatment follow-up period, various measures including survival/disease status, physical exams, QoL assessments, medical resource utilization, and B symptoms were followed every 12 weeks for 36 months, and then every 6 months until first disease progression or study closure. CT scans were also required every 12 weeks for 12 months, and then every 6 months until study closure. However, according to the last protocol amendment, made after study publication, CT scans were no longer necessary during the ongoing extended monitoring period. Rather, disease response is to be documented based on results of any scans performed either as standard of care or according to investigator judgement prior to starting any subsequent anticancer treatment for cHL. Investigators are also asked to document best response to any subsequent salvage treatment as well as any multimodal therapy that includes brentuximab vedotin.[2,3]

Survival of patients was monitored until minimum of 5 years from randomization of the last patient (changed in post-publication protocol amendment to 10 years) or death, whichever occurred first.[2,3]

Sample Size

Sample size was determined based on the primary endpoint of mPFS with approximately 1,240 patients planned for enrolment. To detect a HR of 0.67 in mPFS (assuming an emergent plateau in mPFS rate after 2 years) representing improvement in 2-year mPFS of 73% in the ABVD group compared to 81% in the BV + AVD group, approximately 260 mPFS events were required to achieve 90% power at 1-sided significance level of 0.025 using a log-rank test. With a sample size of 1,240, the study was deemed to have 95% probability of achieving 260 mPFS over 60 months (assuming 36-month accrual, 24 months mPFS follow-up after last patient recruitment, and 5% annual dropout rate). The anticipated total study duration was originally 7 years, with post-publication amendment extending the duration to 14 years.[2,3]

Originally, the protocol specified for a smaller sample size of 1,040 patients but was increased to 1,240 patients in protocol amendment 7 (March 2015) based on externally obtained information. Aggregate data for 299 patients and a 167 patient dataset from the British Columbia Cancer Agency was used by the sponsor to revise projected estimates; the increase in sample size by 200 patients was thought to improve probability to greater than 90% for accruing 260 mPFS events by two years post-randomization of the last patient, compared to three years with 1,040 patients. Updated statistical modeling predicted that approximately 90% of mPFS events occurred within two years of diagnosis, and that a plateau in mPFS rates emerged after approximately two years.[4]

**Study Endpoint and Statistical Analysis**

Primary and Secondary Endpoints

*Primary Endpoint: Modified Progression-Free Survival (mPFS) per IRF*

mPFS was defined as time from date of randomization to the date that the first of the following occurred:

1. Documented disease progression
2. Death due to any cause
3. Modified progression
    - Patients with modified progression was defined as noncomplete responders (Deauville score 3, 4, or 5 on PET scan confirmed by an independent committee) after completion of frontline therapy, who receive anticancer treatment (chemotherapy or RT not specified in the protocol) for HL[2]

Events were assessed by the IRF and according to the Revised Response Criteria for Malignant Lymphoma. This was measured in the ITT population using a stratified log-rank test; stratification was based on region and number of baseline IPFP risk factors. Date of modified progression event was recorded as the first PET scan after completion of frontline therapy that demonstrated absence of complete remission (Deauville score ≥3). A stratified Cox regression model was used to estimate HR and 95% CI for treatment effect, and the K-M approach was used to estimate 2- and 3-year mPFS rates and corresponding 2-sided 95% CIs for each treatment group.[2]

Patients without document mPFS at time of analysis were censored at the date of last response assessment. Details on censoring and how missing data were handled for the primary analysis of mFPS are outlined in the study protocol.[2]

*Sensitivity and Subgroup Analyses*

Modified PFS as measured by investigator was analyzed using the ITT population as part of sensitivity analyses. Additionally, the same primary analysis was performed for the per-protocol population (PP), defined as a subset of ITT patients who do not have a major protocol violation. Several additional exploratory sensitivity analyses were performed to evaluate the robustness of treatment. Analyses on handling of missing assessment and censoring were performed based on one alteration at a time. Various situations were included in this analysis, similar to those used for the primary analysis (but with different progression or censoring rules and outcome) as well as additional situations such as initiation of new anticancer treatment after completion of frontline therapy without confirmed non-complete response.[2]

Analysis of mPFS was also performed for the following pre-defined subgroups: age (< or ≥ 60 years), region (North America, Europe, Asia), Number of IPFP risk factors (0-1, 2-3, 4-7), baseline cancer stage (Stage III, IV), baseline B symptoms (present, absent), PET2 (positive [Deauville score 4-5], negative [Deauville score 1-3]), PET2 Deauville score (<5 or 5), receipt of alternative frontline therapy, and baseline extranodal sites (0, 1, >1).[2] Additional pre-specified subgroups were included approximately one year prior to clinical database lock, without knowledge of treatment efficacy data: mPFS per IRF and mPFS per investigator by age (dichotomized around 45 and 65 years), ECOG PS (0, 1, 2), and gender (male, female).[4] Two exploratory analyses were also performed, one where definition of front-line treatment does not allow for a switch in therapy, and a second analysis for progression-free survival (PFS) defined as documentation of progressive disease or death from any cause, whichever occurs earlier. The exploratory analyses followed similar statistical methods to those used for mPFS.[2]

*Secondary Endpoints*

Key secondary endpoint: overall survival (OS)

OS was defined as time from randomization to the date of death in the ITT population. When there was no documented death at the time of analysis, patients were censored at the date last known to be alive. To compare OS between the two treatments, stratified log-rank test was used. Hazard ratios with 95% CIs were estimated using the Cox regression model, and the K-M approach was used to estimate distribution of OS endpoints for each treatment group. Test for significance was performed (at 1-sided 0.025 level) only if the primary endpoint of mPFS was statistically significant.[2]

A sensitivity analysis was performed using the per-protocol population. Different censoring approaches were also analyzed in the ITT population.[2]

Other secondary efficacy endpoints included:

- Complete remission (CR) based on the ITT population: defined as the proportion of patients who achieved CR at the end of assigned treatment, as determined by an IRF. The CR rates were compared using a stratified Cochran-Mantel-Haenszel (CMH) test, and a logistic regression model was used to estimate the treatment effect (odds ratio). Sensitivity analyses were performed using the response-evaluable population (i.e., patients with measurable disease at baseline, who received at least one dose of study drug and had a minimum of one postbaseline response assessment). A similar analysis was performed for CR as assessed by investigators.
- Objective response rate (ORR) based on the ITT population: defined as CR+PR (partial response) and was compared between the two treatment groups using the stratified CMH test.
- Duration of response (DOR) based on the ITT population: measured in subjects with confirmed response, between first documentation of response and disease progression.
- Duration of complete remission (DOCR) based on the ITT population: measured in subjects with confirmed CR, between first documentation of response and disease progression.
- Event-free survival (EFS) based on the ITT population: defined as time from randomization until treatment failure from any cause (first of disease progression, premature discontinuation of treatment for any reason, or death due to any cause).
- Disease-free survival (DFS) based on the subset of ITT population achieving CR: defined as time from CR to disease progression, death from lymphoma, or acute toxicity from treatment.
- Rate of patients that received consolidating irradiation: was compared between treatment groups using the stratified CMH test[2]

All time-to-event secondary endpoints were analyzed similarly to OS, in order to estimate 2-year event rates for each treatment group and HRs (with 95% CI) between the two treatment groups.[2]

<u>Interim Analyses and Multiplicity</u>

For the primary endpoint of mPFS, two formal interim analyses were planned. The first was a futility analysis, conducted after the first 348 patients had completed their assigned treatment (with no more than 2 missed doses) or had discontinued treatment prior to completion of regimen.[2]

For the key secondary endpoint of OS, an interim analysis was performed at the time of the final mPFS analysis. Final OS analysis was planned for when 112 deaths had occurred (assuming 5-year OS rate of 91% and 88% for BV + AVD and ABVD, respectively; HR=0.75).[2]

mPFS was tested at a 1-sided significance level of 0.025; if statistically significant, OS analysis was also performed at a 1-sided significance level of 0.025. The O'Brien-Fleming boundary with Lan-DeMets alpha-spending function was used to control for overall Type I error.[2] Only the primary and key secondary endpoints were adjusted for multiplicities; for other secondary and exploratory endpoints, p-values were for descriptive purposes only.[8]

Health-Related Quality of Life

Patient-reported outcomes (PROs) and QoL assessments were measured during the treatment phase on Day 1 of each cycle, prior to any other study procedures. These assessments were based on the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30), the Functional Assessment of Chronic Illness Therapy – Dyspnea 10-item short form questionnaire (FACIT-Dyspnea 10), and the abbreviated Functional Assessment of Cancer Therapy/ Gynecologic Oncology Group - Neurotoxicity (FACT/GOG-Ntx Abbreviated). PROs measured using the EORTC-QLQ-C30 were considered part of secondary outcomes, whereas other assessments were considered exploratory. Patient-reported outcomes were also not included in the adjustment for multiplicity. Overall, interpretation of QoL end points is limited.[2]

The EORTC QLQ-C30 contains 30 items spanning five functional scales (i.e., physical, role, cognitive, emotional, social), nine symptoms scales (i.e., fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, financial difficulties), as well as a global health status/QoL scale. The responses are converted into a scale score from 0 to 100; higher scores indicate better QoL for functional and global health status/QoL scales, whereas lower scores indicated better QoL for symptom scales.[47]

The FACIT-Dyspnea 10 consists of two subscales (i.e., dyspnea and functional limitations) containing 10 items each. Patients are asked to evaluate their shortness of breath and difficulty with various functional activities over the past 7 days. A summary score is calculated, with higher scores indicating worse dyspnea or function limitations.[50] The FACT/GOG-Ntx assesses for symptoms of peripheral neuropathy over the past seven days and consists of 38 items spanning five subscales measuring well-being in the physical, social/family, emotional, functional domains, as well as additional neurotoxicity concerns. A summary score is calculated, with higher scores indicating better quality of life.[51] The EQ-5D-3L is a two-part standardized instrument that measures health status, and consists of the EQ-5D descriptive system and EQ visual analogue scale. The descriptive system consists of five dimensions (i.e., mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Patients are asked to describe their health related to each dimension according to three response levels of severity, ranging from no problems, some problems, to extreme problems. A summary index score is derived using value sets that provide weights for each health state description based on preferences of the general population in a specific region or country. The VAS is a subjective quantitative measure of health come and measures a patient's self-rated health on a vertical visual analogue scale, between best to worst health that the patient can imagine.[52]

PROs evaluated by FACIT-Dyspnea 10 and FACT/GOG-Ntx abbreviated were collected until EOT (30 days ± 7 days after last dose of frontline therapy), and data from EORTC QLQ-30 was also collected during the post-treatment follow-up period until the final visit. For patients who discontinued the study drug, collection of PRO data was continued until scheduled study visits were discontinued.

Utility measurement, using the EQ-5D questionnaire, was conducted until either confirmed disease progression or 3 years after last dose of frontline therapy, whichever occurred sooner.[2]

Safety

All patients who received at least one dose of study drug were included in the safety analysis set and were analyzed according to the actual treatment received. AEs were categorized according to the Medical Dictionary for Regulatory Activities (MedDRA) and intensity measured using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03, effective June 14, 2010. Safety parameters collected include incidence, type, and severity of AEs.[2]

Specific safety assessments, including hematology and serum chemistry, weight, BSA, as well as vital signs were measured prior to drug administration on Day 1 and 15 as well as EOT. Changes from baseline in a patient's clinical laboratory results, vital signs, and

weight were also evaluated. Furthermore, on Day 1 of each cycle and at EOT, physical exams, ECOG performance status, QoL assessments, and medical resource utilization were measured.[2]

AEs were recorded from the first dose of study drug through Day 30 after the last dose of frontline treatment; serious adverse events were collected similarly but starting at the time of signing informed consent. However, peripheral neuropathy and treatment-related AEs were followed until resolution or end of study, whichever was sooner.[2]

Protocol Amendments

A total of eight amendments were made to the protocol (original version issued March 29, 2012); seven amendments were made prior to data cut-off and regulatory approval, and an additional amendment was made after study publication to fulfill post-marketing requirements from the United States FDA. Patients were not enrolled into the study until the Amendment 4. Key changes made thereafter which may impact the trial conduct and/or results are summarized in Table 22 below. Although the sample size was increased in Amendment 7, reasons were justified based on additional Canadian data. Overall, the amendments made to the protocol were reasonable and not expected to significantly impact the integrity of the study.

## Table 22: Summary of key protocol amendments

| Amendment Number (Date) | Summary of Key Changes |
|---|---|
| Amendment 4 (August 3, 2012) | • For noncomplete responders at the end of frontline therapy, allowed sites to use PET results (determination of PET positivity) to guide additional RT and doses, as well as allow RT for patients with PET positive residual mass of any size, instead of only those with masses ≥ 2.5cm. |
| Amendment 5 (February 6, 2014) | • Standardized the definition of a missed dose to allow investigators to omit individual agents from a treatment regimen without counting as a missed dose. This provided symmetry between the two treatment groups in the definition for completion of frontline therapy and eliminated potential bias that could favor the experimental treatment group and affect the mPFS. |
| Amendment 6 (May 27, 2014) | • Removed exclusion criteria involving pulmonary carbon monoxide diffusion capacity. This was done to increase the generalizability of the study and to align with standard practice for treatment of patients with advanced HL. |
| Amendment 7 (March 2, 2015) | • Increased sample size by 200 patients to a total of approximately 1,240 enrolled and increased anticipated enrollment period to 3 years to improve likelihood of observing 260 mPFS events.<br>• Sample size was increased from 1,040 to 1,240 patients; from 520 to 620 patients per treatment group. Estimated number of global study sites also expanded from 200 to 250.<br>• Increased anticipated length of enrollment from 2 to 3 years and reduced projected length of follow-up from 3 to 2 years (to maintain the anticipated 5-year total study length to reach the final mPFS analysis).<br>• Revised statistical assumption for mPFS rates such that the primary endpoint is powered on the assumption of a 2-year mPFS of 81% for patients receiving BV + AVD compared to 73% for patients in the ABVD group, rather than the previous assumption of a 3-year mPFS of 82.5% and 75% for each treatment group, respectively.<br>• Revised timing of final OS analysis, so it is conducted when 112 death occur, predicted to be approximately 4 years (instead of 5 years) after randomization of the last patient. |
| Amendment 8* (July 16, 2018) | • Extend duration of monitoring for long-term safety outcomes; reporting of events to occur at 60 months and at minimum 120 months after randomization of the last patient. Outcomes include treatment-related SAEs, treatment-emergent peripheral neuropathy events, secondary malignancies, and deaths.<br>• Monitoring of following efficacy endpoints to continue during posttreatment follow-up:<br>  ○ Response as per investigator assessment on scans performed as standard of care or before initiation of subsequent anticancer therapy for classic HL<br>  ○ Best response as per investigator assessment to subsequent salvage anticancer therapies and to any multimodal treatment including brentuximab vedotin<br>• Altered wording so anticancer therapy received as part of mPFS definition is not strictly chemotherapy or radiotherapy but was generalized to include other treatment such as immunotherapy, which reflected actual study conduct. |

| Amendment Number (Date) | Summary of Key Changes |
|---|---|
| | • Changed wording to reflect that post-treatment follow-up will continue for a minimum of 10 years after enrollment of last patient; total study duration was extended to approximately 14 years.<br>• Requirement for regular CT scans during the post-treatment follow-up phase was removed; physical examinations, including B symptom assessment may continue during the post-treatment follow-up phase if clinically indicated<br>• Specified that EORTC QLQ-C30 questionnaire and utility measurement should continue for 3 years after discontinuation of frontline treatment, and end at post-treatment follow-up Visit 12, disease progression, or start of subsequent anticancer therapy, whichever is sooner. |

*ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine; BSA = body surface area; BV + AVD = brentuximab vedotin plus doxorubicin, vinblastine, dacarbazine; CR = complete remission; EOT = end of treatment; HL = Hodgkin lymphoma; IRF = independent review facility; mPFS = modified progression-free survival; OS = overall survival; PRO = patient reported outcome; RT = radiation therapy; SAE = serious adverse event*

** As Protocol Amendment 8 was created after study publication to fulfill postmarketing requirements from the US FDA, the summary provided in this box is provided solely for information purposes. Only pertinent changes to the protocol, relating to length of follow-up and measure of relevant outcomes are made to the content of this report. Other details such as change in schedule of assessments have not been reflected to preserve accuracy of the study protocol used for generating data that was analyzed in the original study publication.*
*Source: Connors et al. 2018[2] and Sponsor's submission[2,3]*

### b) Populations

A total of 1,334 patients at 218 sites were randomly assigned to receive BV + AVD (664 patients) or ABVD (670 patients) between November 19, 2012 to January 13, 2016. Baseline demographics and characteristics were generally well balanced between the two treatment groups. Overall, the median age of enrolled patients was 36 years (range 18-83 years); most (66%, 874 of 1334) were younger than 45 years and 14% (186 of 1334) were 60 years or older.[2] Of the total number of patients enrolled, 58% (n=776) were male and 84% (n=1114) were White.[2,4] 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.[2] Detailed baseline demographic and clinical characteristics are presented in Table 23.

## Table 23: Baseline Patient Demographics and Characteristics, ITT, Stage III and IV Populations

| Demographics, clinical characteristics | ITT population | | Stage III Only | | Stage IV Only | |
|---|---|---|---|---|---|---|
| | BV + AVD n=664 | ABVD n=670 | BV + AVD n=237 | ABVD n=246 | BV + AVD n=425 | ABVD n=421 |
| Sex – no (%) | | | | | | |
| Male | 378 (57) | 398 (59) | 133 (56) | 154 (63) | 243 (57) | 243 (58) |
| Female | 286 (43) | 272 (41) | 104 (44) | 92 (37) | 182 (43) | 178 (42) |
| Median age (range) - yr | 35 (18-82) | 37 (18-83) | | | | |
| Age categories (yr), n (%) | | | | | | |
| <45 | 451 (68) | 423 (63) | 159 (67) | 162 (66) | 292 (69) | 260 (62) |
| 45-59 | 129 (19) | 145 (22) | 47 (20) | 50 (20) | 82 (19) | 94 (22) |
| 60-64 | 24 (4) | 40 (6) | 8 (3) | 14 (6) | 15 (4) | 25 (6) |
| ≥65 | 60 (9) | 62 (9) | 23 (10) | 20 (8) | 36 (8) | 42 (10) |
| Race, n (%) | | | | | | |
| White | 560 (84) | 554 (83) | 194 (82) | 204 (83) | 364 (86) | 348 (83) |
| Asian | 56 (8) | 57 (9) | 19 (8) | 21 (9) | 37 (9) | 35 (8) |
| Black or African American | 20 (3) | 25 (4) | 10 (4) | 6 (2) | 10 (2) | 19 (5) |
| Other | 18 (3) | 17 (3) | 9 (4) | 5 (2) | 9 (2) | 12 (3) |
| Not reported | 10 (2) | 17 (3) | 5 (2) | 10 (4) | 5 (1) | 7 (2) |
| Regions, n (%) | | | | | | |
| Americas | 261 (39) | 262 (39) | 106 (45) | 120 (49) | 154 (36) | 142 (34) |
| Europe | 333 (50) | 336 (50) | 99 (42) | 97 (39) | 233 (55) | 237 (56) |
| Asia | 70 (11) | 72 (11) | 32 (14) | 29 (12) | 38 (9) | 42 (10) |

| Demographics, clinical characteristics | ITT population | | Stage III Only | | Stage IV Only | |
|---|---|---|---|---|---|---|
| | BV + AVD n=664 | ABVD n=670 | BV + AVD n=237 | ABVD n=246 | BV + AVD n=425 | ABVD n=421 |
| Ann Arbor stage at initial diagnosis, n (%)* | | | | | | |
| Stage I | 0 | 0 | 0 | 0 | 0 | 0 |
| Stage II† | 1 (<1) | 0 | 0 | 0 | 0 | 0 |
| Stage III | 237 (36) | 246 (37) | 237 (100) | 246 (100) | 0 | 0 |
| Stage IV | 425 (64) | 421 (63) | 0 | 0 | 425 (100) | 421 (100) |
| Not applicable, unknown, or missing | 1 (<1) | 3 (<1) | 0 | 0 | 0 | 0 |
| IPS, n (%)‡ | | | | | | |
| 0 or 1 | 141 (21) | 141 (21) | 86 (36) | 97 (39) | 55 (13) | 43 (10) |
| 2 or 3 | 354 (53) | 351 (52) | 128 (54) | 122 (50) | 225 (53) | 227 (54) |
| 4 to 7 | 169 (25) | 178 (27) | 23 (10) | 27 (11) | 145 (34) | 151 (36) |
| ECOG performance status, n (%)§ | | | | | | |
| 0 | 376 (57) | 378 (57) | 154 (65) | 159 (65) | 221 (52) | 217 (52) |
| 1 | 259 (39) | 262 (39) | 76 (32) | 82 (33) | 184 (43) | 181 (43) |
| 2 | 28 (4) | 26 (4) | 7 (3) | 5 (2) | 20 (5) | 22 (5) |
| 3 or 4 | 0 | 0 | - | - | - | - |
| Not obtained or missing | 1 (<1) | 4 <1) | - | - | - | - |
| Bone marrow involvement, n (%) | | | | | | |
| Yes | 147 (22) | 151 (23) | 4 (2) | 11 (4) | 142 (33) | 140 (33) |
| No | 502 (76) | 509 (76) | 230 (97) | 231 (94) | 271 (64) | 276 (66) |
| Unknown or missing | 15 (2) | 10 (1) | 3 (1) | 4 (2) | 12 (3) | 5 (1) |
| Extranodal involvement at diagnosis, n (%) | | | | | | |
| Yes | 411 (62) | 416 (62) | 47 (20) | 57 (23) | 363 (85) | 359 (85) |
| 1 extranodal site | 217 (33) | 223 (33) | 38 (16) | 42 (17) | 178 (42) | 181 (43) |
| >1 extranodal site | 194 (29) | 193 (29) | 9 (4) | 15 (6) | 185 (44) | 178 (42) |
| No | 217 (33) | 228 (34) | 178 (75) | 180 (73) | - | - |
| Unknown or missing | 36 (5) | 26 (4) | 12 (5) | 9 (4) | - | - |
| Patients with any B symptom, n (%)¶ | 399 (60) | 381 (57) | 123 (52) | 124 (50) | 276 (65) | 256 (61) |

*ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine; BV + AV D= brentuximab vedotin plus doxorubicin, vinblastine, dacarbazine; ECOG = Eastern Cooperative Oncology Group; IPS = International Prognostic Score*
Percentages may not total 100 because of rounding.
*The Ann Arbor staging system ranges from I to IV, with higher stages indicating more widespread disease.
†Patients in this category have major protocol violation.
‡The IPS ranges from 0 to 7, with higher scores indicating increased risk of treatment failure. Scores of 0 to 1 denote low risk, scores of 2 to 3 intermediate risk, and scores of 4 to 7 high risk.
§Values for ECOG performance status range from 0 to 5, with higher scores indicating greater disability.
¶B symptoms consist of night sweats, unexplained fever (temperature >38°C), or loss of more than 10% of body weight.
*Source: adapted from Checkpoint Meeting Document, June 2020*[7]

Specific to the funding request of patients with Stage IV disease, which includes 846 patients (425 in the BV + AVD group; 421 patients in the ABVD group), the demographics and baseline characteristics were similar to the overall ITT population and well balanced between treatment groups. However, compared to the overall ITT population, patients with Stage IV disease had higher IPFP risk factors (score 4-7) and had more bone marrow as well as extranodal involvement.[4]

### c) Interventions

Patients in both groups received combination therapy, with each agent administered as an IV infusion on Days 1 and 15 of a 28-day cycle. Treatment was continued up to a maximum of six cycles.[2]

BV + AVD consisted of the following agents, administered in sequential order:

- A: Doxorubicin 25 mg/m$^2$ IV infusion
- V: Vinblastine 6 mg/m$^2$ IV infusion
- D: Dacarbazine 375 mg/m$^2$ IV infusion
  - Then, approximately 1 hour after end of dacarbazine infusion, the following was administered:
- BV: Brentuximab vedotin 1.2 mg/kg IV infusion over approximately 30 minutes[2]

The brentuximab vedotin dose was calculated based on actual weight, except for patients weighing greater than 100kg. In such cases, the dose was calculated based on 100kg. During the trial, 9% of patients (n=58) randomized to BV + AVD received the 100

mg capped dose of brentuximab vedotin.[7] Dose adjustments were performed in patients who experienced a change in weight of ≥10% from baseline.[2]

ABVD consisted of the following agents, administered in sequential order:

A: Doxorubicin 25 mg/m$^2$ IV infusion
B: Bleomycin 10 units/m$^2$ IV infusion
V: Vinblastine 6 mg/m$^2$ IV infusion
D: Dacarbazine 375 mg/m$^2$ IV infusion[2]

Dose modification was permitted, based on treatment-associated toxicity. For example, Grade ≥ 3 nonhematologic AEs led to suspending BV + AVD until improvement seen (≤ Grade 2) or effects returned to baseline. Peripheral neuropathy also had specific modifications outlined in the protocol, including dose reduction of BV to 0.9 mg/kg with Grade 2 severity, or for Grade 3 severity, withholding BV and resuming at a reduced dose upon improvement; Grade 4 peripheral neuropathy led to discontinuation of BV. Also, administration of growth factors (i.e., granulocyte colony stimulating factor [G-CSF] or granulocyte-macrophage colony stimulating factor [GM-CSF]) were permitted to treat neutropenia, as were platelets and/or red blood cell supportive growth factors or transfusions when needed. Due to the higher incidence of neutropenia in the BV + AVD group, the independent data and safety monitoring committee recommended primary prophylaxis with G-CSF for patients newly randomized to BV + AVD treatment. This change was made after 75% of enrolment was complete; primary prophylaxis was defined as use of G-CSF by Day 5 of the treatment cycle.[2]

Prophylactic antiemetics and antidiarrheals were not included in the study protocol but were permitted at the physician's discretion. Corticosteroids were permitted as part of a chemotherapy premedication regimen or for treatment of HL according to an institution's standards.[2]

A PET scan was performed after PET2, on Day 25. If the results showed a Deauville score of 5, physicians had the option of switching the patient's treatment to an alternative regimen. Any switch in therapy made prior to completion of frontline treatment was not considered an mPFS event.[2]

At the end of frontline treatment, patients in partial remission with persistent PET-positive disease were permitted to receive radiation therapy at the discretion of the investigator. However, such patients were counted has having an mPFS event only if they were deemed to have a noncomplete response (i.e., Deauville score ≥3) confirmed by IRF. [2,7]

Completion of Frontline Therapy

Completion of frontline therapy encompassed patients who received only the assigned treatment as well as those who switched regimens. Specifically, in those who did not switch treatment regimens, completion of frontline therapy was defined as administration of planned study drug with no greater than two missed doses. Administration of study drug referred to the full regimen; thus, patients were permitted to miss individual agents within the regimen without it being counted as a missed dose. For patients who switched treatment regimens prior to completing assigned BV + AVD or ABVD, completion of frontline therapy was defined as finishing one alternative anticancer regimen (i.e., chemotherapy or radiation therapy) for HL, after discontinuation of BV + AVD or ABVD.[2]

In both BV + 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 (RDI) of each agent in both groups ranged from 99-100%. During frontline treatment, 15 patients (2%) in the BV + AVD group and 9 patients (1%) in the ABVD group switched to alternative chemotherapy, due to the following reasons: Deauville score of 5 (1 patient in BV + AVD vs. 4 in ABVD group), adverse events (12 patients in BV + AVD vs. 1 in ABVD group), or other reasons (2 patients in BV + AVD vs. 4 in ABVD group).[4] In the BV + AVD group, patients were most commonly switched to ABVD; those in the ABVD group were switched most often to BEACOPP.[8]

In the BV + AVD group, slightly higher proportion of interventions (e.g., dose adjustments, delay, discontinuation, etc.) were reported for BV compared to the other three agents in the combination. During treatment, at least one intervention was reported for the following: 66% of patients on brentuximab vedotin, 54% on doxorubicin, 57% on vinblastine, and 53% of patients who received dacarbazine. Most interventions for brentuximab involved dosage reduction, delay, or discontinuation; the BV component of the combination was discontinued permanently in 71 patients (11%). In the ABVD group, interventions were reported most frequently for

bleomycin. During treatment, at least one intervention was reported for 48% of patients who received bleomycin, 43% on vinblastine, 39% on dacarbazine, and 38% who received doxorubicin. The most common intervention attributed to bleomycin were dose delay and discontinuation. For both treatment groups, the most frequently reported modification overall was a dose delay (BV + AVD 48 to 49% vs. ABVD 32 to 33% of patients for each drug), followed by premature and permanent study drug dose reduction (BV + AVD 4 to 26% vs. ABVD 3 to 9% of patients for each drug) and discontinuation (BV + AVD 6 to 11% vs. ABVD 3 to 16% of patients for each drug). Of all the agents included in the trial, patients requiring a dose reduction (n=170, 26%) was highest for brentuximab vedotin.[2]

G-CSF primary prophylaxis was administered to 83 patients (13%) in the BV + AVD group and 43 patients (7%) who received ABVD treatment. Specific to the BV + AVD group, fewer dose reductions and delays were seen overall in patients who received G-CSF prophylaxis. Concomitant administration or secondary prophylaxis of neutropenia using myeloid growth factors (most commonly filgrastim) was administered to more patients in the BV + AVD group: of the safety population, 536 (81%) in the BV + AVD group and 373 (57%) patients in the ABVD group received at least one growth factor.[4]

Concomitant and Subsequent Medications

At least one concomitant medication was taken by almost all patients (safety population: 100%, n=659 in BV + AVD vs. 99%, 653 patients in ABVD). More than 25% of patients in each group had received ondansetron, dexamethasone, metoclopramide, acetaminophen, lorazepam, filgrastim, or allopurinol. Additionally, 26% of patients in the BV + AVD group received sodium chloride, and 25% of patients in the ABVD group received sulfamethoxazole/trimethoprim.[4]

Overall, after completion of frontline therapy, 18% of patients in the BV + AVD group (n=121) received at least one subsequent anticancer therapy compared to 22% (n=144) in the ABVD group. The most common subsequent therapy was chemotherapy (n=66, 10% in BV + AVD group; n=99, 15% in ABVD).[4] Agents most commonly used by the BV + AVD group were cisplatin, cytarabine, dexamethasone combination (n=16, 2%) or carboplatin, etoposide, ifosfamide combination (n=10, 2%). In the ABVD group, patients were most often switched to brentuximab vedotin (n=39, 6%).[8] Other treatment included consolidative radiation therapy (n=52; 8% in each group) and high-dose chemotherapy in combination with transplant (n=36, 5% for BV + AVD; n=54, 8% ABVD group).[4] Immunotherapy was also received by 2% of patients in each treatment group (n=10 in BV + AVD; n=16 in ABVD), and <1% in each group received chemotherapy plus radiation.[2] Details of subsequent anticancer treatment in patients who experienced modified progression (i.e., as part of primary endpoint) are discussed below under Efficacy Outcomes in section 6.3.2.2.

At the end of randomized treatment, a high proportion of patients had achieved complete remission (CR) according to the IRF in both treatment groups: 488 patients (73%) in the BV + AVD group and 472 patients (70%) in the ABVD group. Of patients who achieved CR, 22 patients (3%) in the BV + AVD group and 24 patients (4%) in the ABVD group subsequently received at least one anticancer therapy as a result of disease progression (according to investigator). Most patients who had progressed after achieving CR were started on chemotherapy (n=18 BV + AVD; n=22 ABVD). The most frequently prescribed subsequent chemotherapy regimens in the BV + AVD group who progressed after achieving CR were combinations of cisplatin, cytarabine, dexamethasone (n=4), carboplatin, etoposide, ifosphamide (n=3), or cisplatin, cytarabine, etoposide, methylprednisolone (n=3). In the ABVD group, the specific combination of carboplatin, etoposide, ifosphamide was administered most often (n=4), though collectively, brentuximab-based regimens were prescribed most frequently (n=10). BV monotherapy was administered to four patients and an additional two received BV maintenance after transplant; combination of BV plus bendamustine was prescribed to 3 patients, whereas one patient was given BV + nivolumab as subsequent treatment to patients in the ABVD group. Twenty-six patients (n=12 BV + AVD, n=14 ABVD) received high-dose chemotherapy plus transplant, with the most common regimens consisting of gemcitabine, cisplatin, dexamethasone with autologous stem cell transplant (ASCT) in the BV + AVD group, and carmustine, etoposide, cytarabine, melphalan along with ASCT in the ABVD group. Radiation was administered to two patients in the BV + AVD group and three patients in the ABVD group, and nivolumab monotherapy was prescribed to two patients in the BV + AVD group and one patient in the ABVD group.[7]

### d) Patient Disposition

The patient disposition diagram for the overall study is outlined in Figure 3. A total of 1,585 patients were screened and 251 patients were excluded for not meeting eligibility criteria: 187 did not meet inclusion criteria and 64 had at least one exclusion criteria. A total of 1,334 patients were randomized to treatment with either BV + AVD (n=664) or ABVD (n=670).[4] Overall, of the 664 patients randomized to the BV + AVD treatment group, 593 patients discontinued study treatment after completing the maximum number of cycles per protocol whereas 71 discontinued treatment due to reasons such as adverse events, progressive disease, withdrawal by

patient, and others. Of the 670 patients randomized to the ABVD group, 608 completed maximum number of cycles per protocol whereas 62 discontinued treatment due to reasons such as adverse event, progressive disease, and withdrawal by patient. At the time of data cut-off on April 20, 2017, 91 patients (14%) in the BV + AVD group and 123 patients (18%) in the ABVD group had discontinued from the study.[2,4]

*Frontline Therapy*

In the BV + AVD group, 629 of 664 patients (95%) completed study treatment per protocol, which encompasses patients who completed any frontline therapy (n=609, 92%), as well as those who experienced progressive disease or died prior to completing first-line therapy (n=20, 3%).[2] Thirty-six patients (5%) did not complete study treatment according to protocol, mainly due to adverse events (n=11), investigator discretion (n=4), or subject withdrawal (n=7).[7] Of the 609 patients who completed first-line therapy, 594 patients (98%) received only the randomized regimen and 15 patients (2%) had switched treatment to complete frontline therapy with an alternative regimen. In other words, overall, 90% of randomized patients (594 of 664) received and completed frontline therapy only with BV + AVD.[2]

In the ABVD group 634 of 670 patients (95%) completed study treatment per protocol: 622 patients (93%) completed any frontline therapy and 12 patients (2%) experienced progressive disease or died prior to completing first-line therapy.[2] Thirty-six patients (5%) did not complete study treatment according to protocol, mainly due to adverse event (n=5) or withdrawal by subject (n=15).[7] Of the 622 patients who completed frontline therapy, 613 patients (99%) received only the randomized regimen and 9 patients (1%) had switched treatment to complete frontline therapy with an alternative regimen. In other words, overall, 92% (613 of 670) received and completed frontline therapy only with ABVD.[2]

Although the reasons for patients not completing study treatment per protocol were generally similar between the two groups, there was a higher number of patients in the BV + AVD group who discontinued protocol treatment due to progressive disease or death, adverse event, or according to investigator discretion; on the other hand, a higher proportion of patients in the ABVD group discontinued protocol treatment due to withdrawal by subject.[2,7]

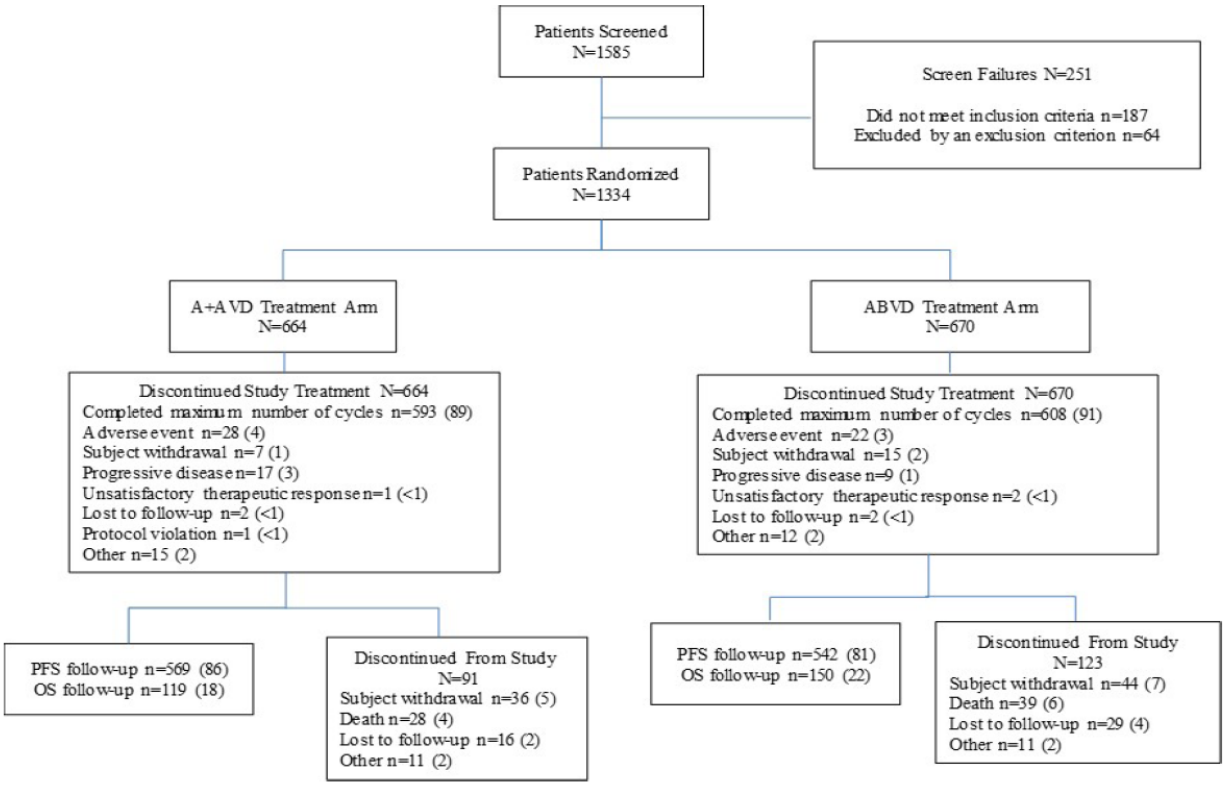
Protocol Deviations

Two categories of major protocol deviations were identified:

- Patients who were enrolled despite not meeting eligibility criteria: n=4 (0.6%) in BV + AVD; n=12 (1.8%) in ABVD groups
- Patients who received incorrect dose or treatment: n=9 (1.4%) in BV + AVD; n=2 (0.3%) in ABVD groups[4]

Given the low numbers, these protocol deviations are not expected bias the trial results.

## Figure 3. Study Subject Disposition at Data Cut-off




*Note: BV + AVD appears as A+AVD in the figure.*
Source: European Medicines Agency. European Public Assessment Report (EPAR) 2018, p.44[4]

### e) Limitations/Sources of Bias

Overall, the ECHELON-1 trial was a well-designed RCT and there were no major concerns with the conduct of the trial. The randomization method and sample size were adequate, and a stratified randomization procedure was used based on known prognostic factors to minimize potential imbalances between the study groups that might lead to biased results. Eligibility criteria were well defined and appropriate; the study population characteristics reflect patients who would be eligible for BV + AVD in Canadian practice, and baseline characteristics between groups were generally well balanced. The populations used for analyses were appropriate, with the key efficacy analysis conducted according to the ITT principle. The study protocol was approved by institutional review boards and ethics committees at each study center and the trial was conducted in accordance with Good Clinical Practice guidelines. However, the following limitations and potential sources of bias of the ECHELON-1 trial were noted by the CADTH Methods Team:[1-4,7,8,48]

- One key issue to note is that the population of the ECHELON-1 trial is broader than the reimbursement request in this CADTH submission. Patients with Stage III and IV were eligible for inclusion into the trial. However, this reimbursement request is limited to patients with Stage IV disease only. Therefore, the request is for a subpopulation of the trial and not for the ITT population. 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 Health Canada (HC) approved indication was limited to patients with Stage IV, although the Sponsor's request to HC included the full trial population. It appears that a precautionary approach was taken due to uncertainties regarding efficacy (including inconsistency in observed mPFS benefit between Stage III and IV subgroups, immature OS data, and use of surrogate endpoint); 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 patients. HC provided an approved indication for Stage IV disease, based on an overall positive study with inconsistent results from key subgroups but a trend for positive mPFS for Stage IV patients.
The updated efficacy analysis performed after 3- and 4-years patient follow-up reported traditional PFS, which was an exploratory analysis. This longer follow-up data had not been included in the HC assessments. These updated results should be interpreted with caution as the protocol did not require additional response assessments after an mPFS event was documented; thus, study conduct around the mPFS endpoint had potential to impact identification of a PFS event. Furthermore, the updated analyses report PFS as assessed by investigators, which is subject to bias. Nevertheless, the latest available data for the post-hoc PFS analyses showed that the magnitude of benefit with both Stage III and IV disease were consistent with the ITT population and favoured BV + AVD, which appears to be reflective of benefit seen over a longer time frame.

- Open-label treatment protocol (also susceptible to reporting and performance bias); as an unblinded study, 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; the IRF that measured the primary outcome were blinded to treatment assignments to reduce investigator bias. IRF results were not available to study investigators but, there is still potential for bias from the treating physicians, who may administer subsequent treatment preferentially or based on the impression of the treatment group which a patient was enrolled in. The magnitude and direction of this bias is uncertain, although it is plausible that this would be in favour of new treatment, as well as potentially impact overall survival.
- According to the CGP, measured outcomes were clinically important and relevant to patients with cHL. The primary endpoint selected by investigators is novel and includes modified progression in order to capture all events that reflect a failure of frontline chemotherapy. It is recognized that modified progression-free survival was included to accurately evaluate the curative intent of frontline treatment by identifying patients who receive additional treatment due to noncomplete response, and to reduce confounding that may impact traditional PFS; however, this makes cross-trial comparisons (to trials reporting on traditional PFS) difficult. Nevertheless, mPFS results were numerically more conservative than those seen in the exploratory analysis of traditional PFS. Also, the strength of the association between PFS as a surrogate outcome and OS is unknown.
- Only the primary and key secondary endpoints were adjusted for multiplicities; for other secondary and exploratory endpoints, p-values are for descriptive purposes only and were not controlled for Type 1 error. This includes data from PROs and HRQoL measures. Subgroup and sensitivity analyses were prespecified, though were considered exploratory and were also not adjusted for multiplicity. The primary endpoint was supported by several consistent sensitivity analyses; however, results from subgroup analyses were inconsistent.
- Final analysis of OS, a key secondary outcome, was scheduled for after 112 deaths, which have yet to occur (67 deaths occurred by data cut-off). Current OS data is still immature (i.e., medians not met in either study group) and reflects interim analysis.
- Specific dose adjustment for BV was provided in the study protocol; AVD and ABVD treatment were modified based on the corresponding label/monograph. Within each treatment group, brentuximab and bleomycin involved a higher number of dosage interventions compared to the other agents, and of all the agents included in the trial, the proportion of patients requiring a dose reduction was highest for brentuximab vedotin. In patients treated with BV + AVD, the BV component was discontinued permanently in 71 patients (11%); as the rest of treatment could be continued without counting as a missed dose, this may impact results (e.g., favour control group) as patients were not receiving the full regimen, particularly the study drug in question.
- Switch to alternate treatment was permitted according to physician discretion, based on cycle 2 PET scan results. However, only a small proportion of patients had switched to alternative frontline therapy (BV + AVD: n=15, 2%; ABVD: n=9, 1%) thus switching therapy likely had little effect on overall outcomes. The low numbers also appear to indicate limited interest by treating physicians in escalating the regimen based on an interim positive PET result; according to the CGP, a positive result on an interim PET-scan does not necessarily indicate a true failure of front-line therapy.
- During the study follow-up period, all patients were permitted to receive subsequent treatment for HL, which included brentuximab vedotin (e.g., 39 patients [6%] in ABVD group). Overall, 18% of patients in the BV + AVD group and 22% in the ABVD group received at least one subsequent anticancer therapy. This may confound the assessment of OS by prolonging survival beyond what would have occurred with frontline treatment alone.

- At the end of frontline treatment, patients in partial remission with persistent PET-positive disease were permitted to receive radiation therapy at the discretion of the investigator; this was counted as an mPFS event only if the patient was deemed to have a noncomplete response (Deauville score ≥3) that was confirmed by IRF. Receipt of subsequent RT without counting as an event could have potential to confound overall benefit of each treatment, though the occurrence of this was fairly low (n=43, 6% in BV + AVD; n=34, 5% ABVD) and administration of adjuvant RT is often done in practice as part of curative treatment. Additionally, in an unblinded trial setting, there is potential for bias by the treating physician to administer radiation treatment to a greater number of patients in one favoured treatment group. However, radiation therapy was given as first subsequent therapy in a similar number of patients in each group (BV + AVD: n=45, 7%; ABVD: n=41, 6%). Furthermore, according to the CGP, there is an inconsistency with the Deauville Score that was considered as a positive (i.e., noncomplete responders) at the end of treatment compared to current Canadian practice. In general, a Deauville Score of 1 to 3 is considered as a negative PET-scan result and 4 to 5 is considered a positive PET-scan result. By including patients with DS of 3, and in an unblinded trial setting, there is potential for bias by the treating physician, for example to administer RT to a greater number of patients in the control group. However, the number of patients who achieved a Deauville Score of 3 plus received subsequent RT (and counted as an mPFS event) was low with little difference between the two groups: n=2 (0.3%) in BV + AVD; n=3 (0.4%) in the ABVD group.
- Rate of hospitalization (37% in BV + 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 group (15%, vs. 9% in the BV + AVD group) were also greater than normally expected in the Canadian patient population.

#### 6.3.2.2 Detailed Outcome Data and Summary of Outcomes

**Efficacy Outcomes**

Efficacy analyses were performed using the ITT population, which included all patients randomized to treatment and analyzed according to the treatment group they were randomized to.[2] The median duration of follow-up was 24.6 months (range 0 to 49), at the data cut-off date of April 20, 2017.[2,4]

Primary Endpoint – Modified Progression-Free Survival (mPFS)

As of the data cut-off date, median mPFS had not been reached in either treatment group.[2] Overall, 263 mPFS events had been observed: 117 (17.6%) in the BV + AVD group and 146 (21.8%) in the ABVD group.[4] The 2-year mPFS rate was 82.1% (95% CI, 78.8 to 85.0) in the BV + AVD group compared to 77.2% (95% CI, 73.7 to 80.4) in ABVD, with a 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 for patients treated with BV + AVD compared to ABVD.[2] The most common reason for being censored in both treatment groups was no documented mPFS event.[4] Specific events and details are outlined in Table 24.

There was a 91% concordance between independent review and investigator determination of mPFS; investigator-assessed 2-year mPFS was 81% (95% CI, 77.6 to 83.9) in the BV + AVD group and 74.4% (95% CI, 70.7 to 77.7) in the ABVD group, resulting in 28% risk reduction (HR=0.72; 95% CI, 0.57 to 0.91; p=0.006).[2] The K-M curves for mPFS based on IRF and investigator assessments are shown below in Figure 4. The vertical drop seen at the end of the curve in the experimental group (denoted as A+AVD in the figure) is a result of events observed in the small number of patients remaining at risk and is not an accurate representative of treatment effect at this time point.

## Table 24: mPFS According to IRF, ITT population

| | A+AVD N=664 | ABVD N=670 |
|---|---|---|
| mPFS, months | | |
| Number with events (%) | 117 (18) | 146 (22) |
| Reason leading to mPFS event | | |
| Progressive disease | 90 (14) | 102 (15) |
| Death due to any cause | 18 (3) | 22 (3) |
| Receipt of additional therapy after non-CR (a) | 9 (1) | 22 (3) |
| Number censored (%) | 547 (82) | 524 (78) |
| 25th percentile (95% CI) | 48.2 (30.9, NE) | 25.6 (15.8, NE) |
| Median (95% CI) | NE (48.2, NE) | NE (NE, NE) |
| 75th percentile (95% CI) | NE (48.2, NE) | NE (NE, NE) |
| Min, max | 0.0*, 48.5* | 0.0*, 49.0* |
| Hazard Ratio (95% CI)(b) | 0.770 (0.603, 0.983) | |
| P-value | 0.035 | |
| Kaplan-Meier estimates (95% CI) (c) | | |
| 1 Year | 85.8 (82.8, 88.3) [n=513] | 80.7 (77.4, 83.6) [n=474] |
| 2 Years | 82.1 (78.8, 85.0) [n=309] | 77.2 (73.7, 80.4) [n=292] |
| 2.5 Years | 80.4 (76.8, 83.6) [n=169] | 74.7 (70.8, 78.2) [n=153] |
| 3 Years | 78.8 (74.8, 82.3) [n=77] | 74.7 (70.8, 78.2) [n=62] |
| Median mPFS follow up (months) (d) | 24.6 | 24.6 |
| (95% CI) | (24.44, 24.84) | (24.48, 24.87) |
| Reason for censoring | | |
| No Baseline and/or no post-Baseline assessment | 11 (2) | 24 (4) |
| mPFS event after more than 1 missed visit | 1 (<1) | 3 (<1) |
| Treatment discontinuation for undocumented disease progression | 4 (<1) | 4 (<1) |
| Loss to follow-up | 14 (2) | 22 (3) |
| Withdrawal by subject | 24 (4) | 24 (4) |
| No documented mPFS event | 493 (74) | 447 (67) |

*Note: BV + AVD appears as A+AVD in the table*
Source: EPAR 2018, p.53[4]

## Figure 4. Kaplan-Meier estimates of mPFS, ITT population

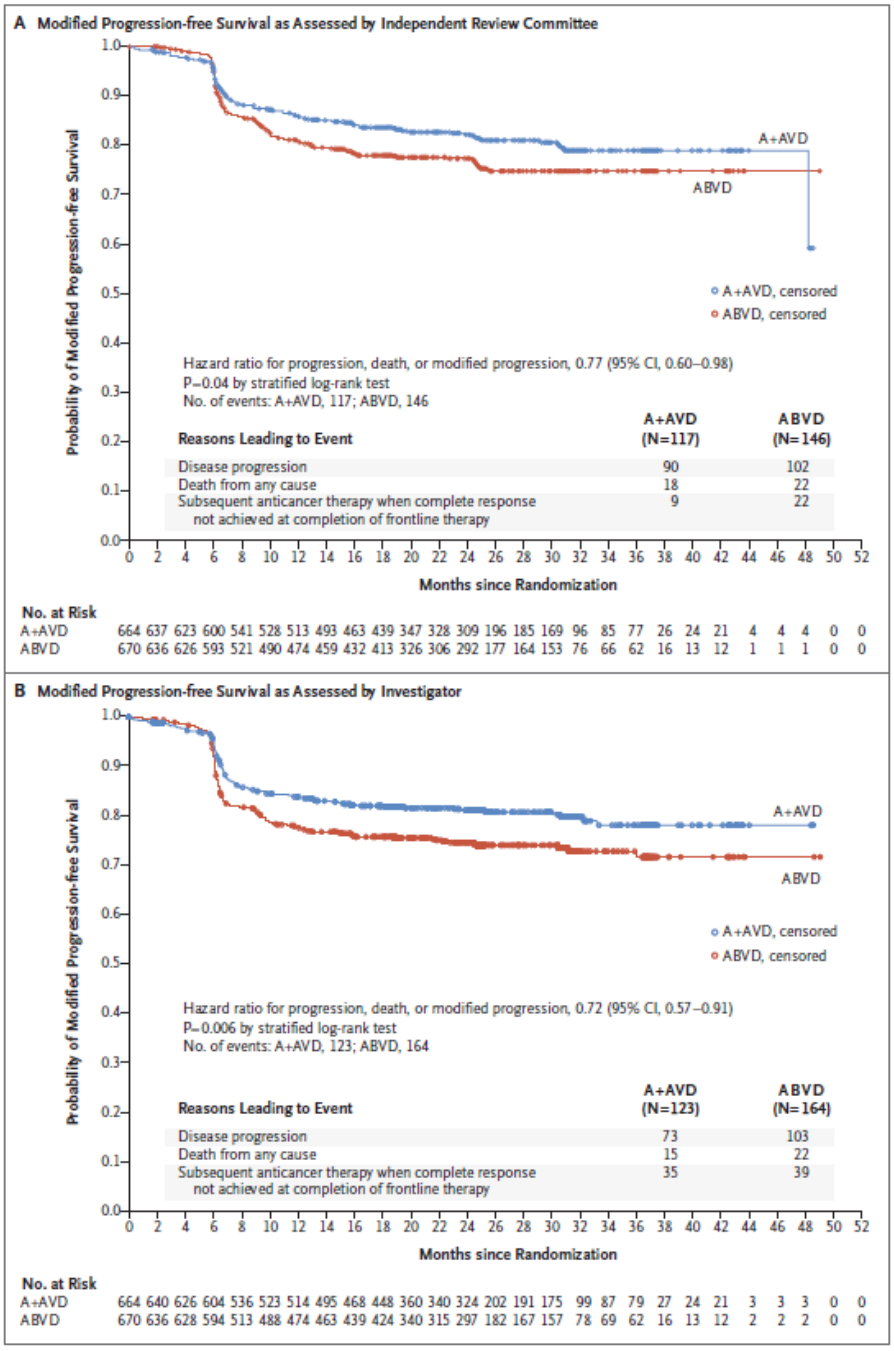



**Figure 1 (facing page). Modified Progression-free Survival in the Intention-to-Treat Population.**

Panel A shows Kaplan–Meier estimates of modified progression-free survival, by treatment group, according to the independent review committee. The hazard ratio for treatment with A+AVD versus ABVD and the 95% confidence intervals (CIs) were based on a stratified Cox proportional-hazards regression model, with treatment as the explanatory variable. Stratification factors included region and International Prognostic Score risk group at baseline. Panel B shows Kaplan–Meier estimates of modified progression-free survival, by treatment group, according to investigators. In Panels A and B, circles indicate censored data. A+AVD denotes brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine, and ABVD doxorubicin, bleomycin, vinblastine, and dacarbazine.

*Note: BV + AVD appears as A+AVD in the figure.*
Source: From the New England Journal of Medicine, Connors JM et al., Brentuximab vedotin with chemotherapy for stage III or IV Hodgkin's lymphoma, 378, 331-344. Copyright ©2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[2]

At the end of the treatment period, 58 patients (19 in BV + AVD, 39 in ABVD) had not experienced disease progression but were considered "at risk" of a modified progression event as these patients had a Deauville score ≥3 (noncomplete response) and no progressive disease. However, only 31 of the 58 patients (9 patients in BV + AVD and 22 patients in ABVD group) had experienced a modified progression as they had additionally received subsequent anticancer regimen. Of those who experienced a modified progression event, 7 out of 9 patients in the BV + AVD group and 15 out of 22 patients in the ABVD group received subsequent salvage chemotherapy, and the remainder (2 patients in BV + AVD, 7 patients in ABVD) received radiation therapy. In patients who experienced modified progression, the Deauville score at the end of treatment was generally 4 or 5. A Deauville score of 3 was noted in 7 of 31 patients (23%); score of 4 in 10 of 31 patients (32%), and score of 5 in 14 out of 31 patients (45%). Of the seven patients who had a Deauville score of 3 and experienced a modified progression event, two patients were in the BV + AVD group (both received radiotherapy), and five were in the ABVD group (2 received salvage chemotherapy; 3 received RT). The most common first subsequent chemotherapy regimen in the BV + AVD group was cisplatin, cytarabine, dexamethasone combination (n=3) and carboplatin, etoposide, ifosfamide combination (n=2). Similarly, in the ABVD group, the most common regimen were the aforementioned combinations (n=3 and 2 patients, respectively), as well as the combination of cisplatin, cytarabine, etoposide, methylprednisolone (n=3). Two patients in the ABVD group subsequently received brentuximab vedotin, either alone or in combination with bendamustine + autologous stem cell transplant (one patient each).[2]

Overall, radiation therapy was given as first subsequent therapy in a total of 45 patients (7%) in the BV + AVD group and 41 patients (6%) in the ABVD group. As mentioned above, two patients (<1%) in the BV + AVD group and seven patients (1%) in the ABVD group were considered to have experienced a modified progression event. The remaining 43 patients (6%) in the BV + AVD group and 34 patients (5%) in the ABVD group received consolidative radiation therapy as per investigator's discretion, but were not considered to have experienced modified progression, as they did not meet the definition of noncomplete response per IRF (i.e., had Deauville scores 1-2).[7]

Sensitivity and Subgroup Analyses

Results of pre-specified sensitivity analysis of mPFS, including alteration of censoring rules and handling of missing data were generally consistent with the primary analysis and favoured treatment with BV + AVD.[4]

Prespecified subgroup analyses of mPFS was performed and can be seen in Figure 5. Most point estimates of hazard ratios for the subgroups suggested benefit with BV + AVD, and were consistent with the ITT population, with some subgroups of patients appearing to derive more benefit with BV + AVD compared with ABVD than others. However, it is important to note that 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. The confidence intervals did not cross the line of unity (1.0) for the following subgroups, suggesting benefit of BV + AVD over ABVD:

- Age < 60 (HR 0.73; 95% CI, 0.56 to 0.96)
- Age < 65 years (HR 0.74; 95% CI, 0.57 to 0.96)
- Geographic location - Americas (HR 0.65; 95% CI, 0.44 to 0.97)
- Geographic location - North America (HR 0.60; 95% CI, 0.39 to 0.90)
- Baseline Ann Arbor Stage IV (HR 0.71; 95% CI 0.53 to 0.96)
- Male (HR 0.70; 95% CI 0.51 to 0.97)[2]

The hazard ratio point estimates for some groups were 1.0, suggesting similar efficacy between treatment groups, and thus no treatment benefit with BV + AVD over ABVD. These subgroups included age ≥60 years, age ≥65 years, and having no extranodal sites at baseline. According to the forest plot below, it appears that treatment with BV + AVD may be more effective in younger patients (e.g., < 65 years of age), and that the subgroups of older patients did not show a treatment benefit (e.g., ≥65 years; HR 1.01;

95% CI 0.53 to 1.94). However, small sample sizes, wide confidence intervals, and high rate of censoring contribute to the uncertainty and caution is required in interpretation of these data.[2]

## Figure 5. mPFS per IRF Assessment in Baseline Risk Factor Subgroups, ITT population

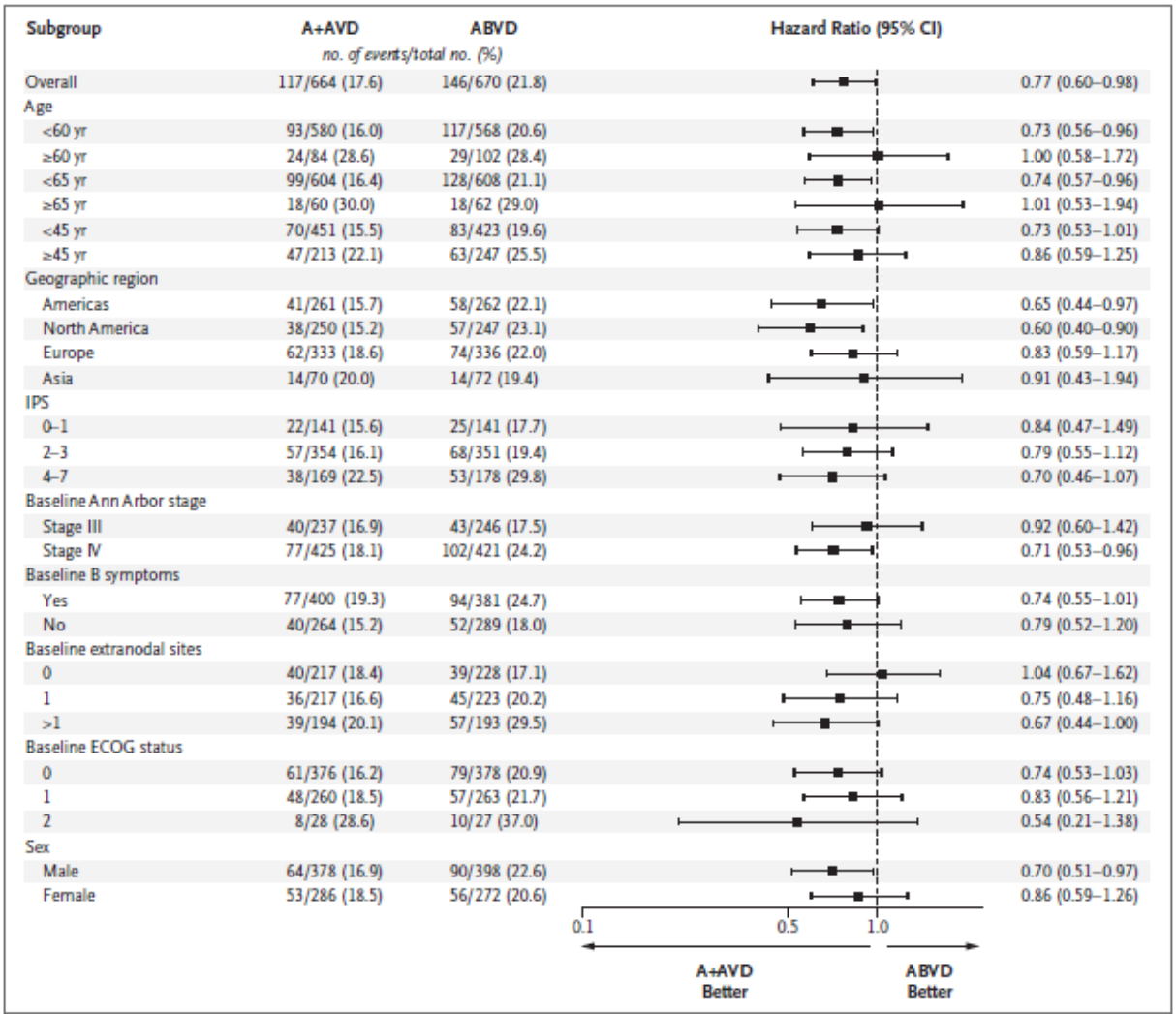



**Figure 2. Forest-Plot Analysis of Modified Progression-free Survival.**

This forest plot shows modified progression-free survival according to the independent review committee in key prespecified subgroups. The hazard ratio for treatment with A+AVD versus ABVD and the 95% confidence intervals (CIs) were based on an unstratified Cox proportional-hazards regression model, with treatment as the explanatory variable. The intention-to-treat population included all the patients who underwent randomization. The International Prognostic Score (IPS) ranges from 0 to 7, with higher scores indicating increased risk of treatment failure: low risk, 0 or 1; intermediate risk, 2 or 3; and high risk, 4 to 7. The Ann Arbor staging system ranges from I to IV, with higher stages indicating more widespread disease. B symptoms consist of night sweats, unexplained fever (temperature >38°C), or loss of more than 10% of body weight. Values for the Eastern Cooperative Oncology Group (ECOG) performance status range from 0 to 5, with higher scores indicating greater disability.

*Note: BV + AVD appears as A+AVD in the figure.*

Source: From the New England Journal of Medicine, Connors JM et al., Brentuximab vedotin with chemotherapy for stage III or IV Hodgkin's lymphoma, 378, 331-344. Copyright ©2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[2]

Clinical Stage at Baseline

Since the funding request pertains specifically to patients with Stage IV disease at baseline, relevant outcomes based on the clinical stage of disease (Stage III or IV) will be discussed in further detail. Of the patients included in the ITT population, a total of 483 (36.2%) had Stage III disease and 846 (63.4%) had Stage IV disease.[2]

*Stage III cHL*

In the ITT population, there were 237 patients in the BV + AVD group and 246 patients in the ABVD group who had Stage III disease at initial diagnosis.[2] No information was available on the number of patients with Stage III disease who received subsequent treatment.

In patients with Stage III disease the 2-year rate without mPFS events was 82.1% (95% CI, 76.0 to 86.8) for those who received BV + AVD (104 patients at risk), compared to 81.0% (95% CI, 75.1 to 85.6) for patients treated with ABVD (106 patients at risk). This corresponds to a 7.8% risk reduction in mPFS events for those treated with BV + AVD compared to patients who received ABVD (unstratified HR 0.92; 95% CI, 0.60 to 1.41).[4]

*Stage IV cHL*

In the ITT population, there were 425 patients in the BV + AVD treatment group and 421 patients in the ABVD group who had Stage IV disease at initial diagnosis.[2] After completing treatment, 45 patients randomized to BV + AVD group received subsequent salvage chemotherapy compared to 69 patients randomized to ABVD; high-dose chemotherapy with transplantation was received by 29 and 37 patients in the BV + AVD and ABVD groups, respectively.[4]

In patients with Stage IV disease the 2-year rate without mPFS events was 82.0% (95% CI, 77.8 to 85.5) for patients in the BV + AVD group (205 patients at risk), and 75.3% (95% CI, 70.6 to 79.3) in the ABVD group (186 patients at risk). This corresponds to a 28.9% risk reduction in mPFS events for patients who received BV + AVD, compared to those treated with ABVD (unstratified HR=0.71; 95% CI, 0.53 to 0.96). [4]

Key Secondary Endpoint – Overall Survival (OS)

As mPFS analysis was statistically significant, OS results were subsequently tested; however, at the time of data cut-off, OS data was still immature (medians not reached). A total of 67 deaths had occurred, 28 deaths in the BV + AVD group and 39 deaths in the ABVD group.[4] The interim 2-year OS rate was 96.6% (95% CI, 94.8 to 97.7) in the BV + AVD treatment group and 94.2% (95% CI, 92.0 to 95.9) in the ABVD group. This corresponds with a 27% reduction in death, favouring BV + AVD (HR=0.73; 95% CI, 0.45 to 1.18, p=0.20).[2] The K-M estimates of the 3-year OS rate was 94.4% for patients in the BV + AVD group and 92.9% in the ABVD group.[4]

*OS Subgroup Analyses*

In patients with Stage III cHL, there were 14 deaths (5.9%) in the BV + AVD group and 12 deaths (4.9%) In the ABVD group. For patients with Stage IV cHL, deaths were reported in 14 (3.3%) and 26 (6.2%) patients in BV + AVD and ABVD groups, respectively. Median OS was not reached in either subgroup of patients.[4]

According to the EMA Assessment report, a post-hoc subgroup analyses for patients with Stage IV disease showed that the 2-year OS rate was 97.4% (95% CI, 95.3 to 98.5) for patients treated with BV + AVD, and 93.4% (95% CI, 90.3 to 95.6) for patients who received ABVD. Compared to the overall ITT population, the unstratified HR (0.51; 95% CI, 0.27 to 0.97) suggested a larger benefit with BV + AVD in patients with Stage IV disease. On the contrary, patients with Stage III disease had estimated 2-year OS rate of 95.1% (95% CI, 91.4 to 97.3) in the BV + AVD group and 95.6% (95% CI, 91.9 to 97.6) in the ABVD group, corresponding to HR of 1.22 (95% CI, 0.56 to 2.63) favouring ABVD.[4]

Exploratory Secondary Endpoints

*Complete Remission (CR)*

Another secondary endpoint is CR rate, as evaluated by IRF. In the ITT population, the CR rate after two cycles of treatment was 69% in the BV + AVD group and 67% in the ABVD group. After receiving randomized treatment, the CR rate in patients treated with

BV + AVD was 73.5% (n=488), compared to 70.4% (n=472) treated with ABVD; with corresponding relative risk (RR) of 1.04 (95% CI, 0.97 to 1.11).[4]

Similar results were seen in patients with Stage IV disease at baseline; the CR rate at the end of randomized treatment was 70.1% (298 of 425) in the BV + AVD group and 68.6% (289 of 421) in the ABVD group; RR 1.02 (95% CI, 0.93 to 1.12). In patients with Stage III cHL at baseline, CR rates at the end of randomized regimen were 79.7% (189 of 237) in the BV + AVD group and 74.4% (183 of 246) in the ABVD treatment group, with RR of 1.07 (95% CI, 0.97 to 1.18).[4]

For CR assessments at the end of randomized treatment regimen, there was an overall concordance rate of 75% between IRF and investigator assessments.[4]

*Objective Response Rate (ORR)*

At the end of randomized treatment, the objective response rate achieved by patients in both treatment groups were similar. The rates, as measured by IRF, were 86% (n= 569) in patients randomized to BV + AVD and 83% (n=553) of patients in the ABVD group. Results of selective secondary endpoints for the ITT population, including ORR, are reported in the table below (Table 25).

## Table 25: CR Rate, ORR, PET Negativity Rate, and Deauville Score per IRF - ITT population

| | A+AVD N=664 n (%) | ABVD N=670 n (%) | Relative Risk (95% CI) |
|---|---|---|---|
| CR rate at the end of randomized regimen (a) | 488 (73) | 472 (70) | 1.042 (0.97, 1.11) |
| CR rate at the end of frontline therapy (b) | 488 (73) | 474 (71) | 1.038 (0.97, 1.11) |
| ORR at the end of randomized regimen (c) | 569 (86) | 553 (83) | 1.038 (0.99, 1.09) |
| PET negativity rate at Cycle 2 (d) | 588 (89) | 577 (86) | 1.028 (0.99, 1.07) |
| Summary of Deauville score at Cycle 2 (e) | | | |
| 1 | 435 (66) | 414 (62) | |
| 2 | 131 (20) | 133 (20) | |
| 3 | 22 (3) | 30 (4) | |
| 4 | 26 (4) | 28 (4) | |
| 5 | 21 (3) | 30 (4) | |
| Rate of Deauville score ≤3 at the end of frontline therapy | 570 (86) | 551 (82) | 1.044 (1.00,1.09) |
| Rate of Deauville score ≤2 at the end of frontline therapy | 563 (85) | 537 (80) | 1.058 (1.01,1.11) |

Note: BV + AVD appears as A+AVD in the figure.
*Source: EPAR 2018, p.63*[4]

Exploratory Subset Analysis: Progression-Free Survival (PFS)

To note, results of exploratory PFS analyses should be interpreted with caution as the protocol did not require additional response assessments after an mPFS event was documented; thus, study conduct around the mPFS endpoint had potential to impact identification of a PFS event. The median PFS estimates was not reached for either treatment group; at a median follow-up of 25 months, 238 PFS events were observed according to IRF assessment, and 241 PFS events were identified by investigators.

The 2-year PFS rate according to IRF was 83.1% (95% CI, 79.8 to 85.9) for BV + AVD patients and 79.8% (95% CI, 76.3 to 82.8) for ABVD patients, corresponding to a stratified HR of 0.83 (95% CI, 0.64 to 1.07). Progressive disease was recorded in 14% (92 of 664 patients) in the BV + AVD group and 16% (106 of 670 patients) in the ABVD group; death due to any cause occurred in 3% of patients in each group.

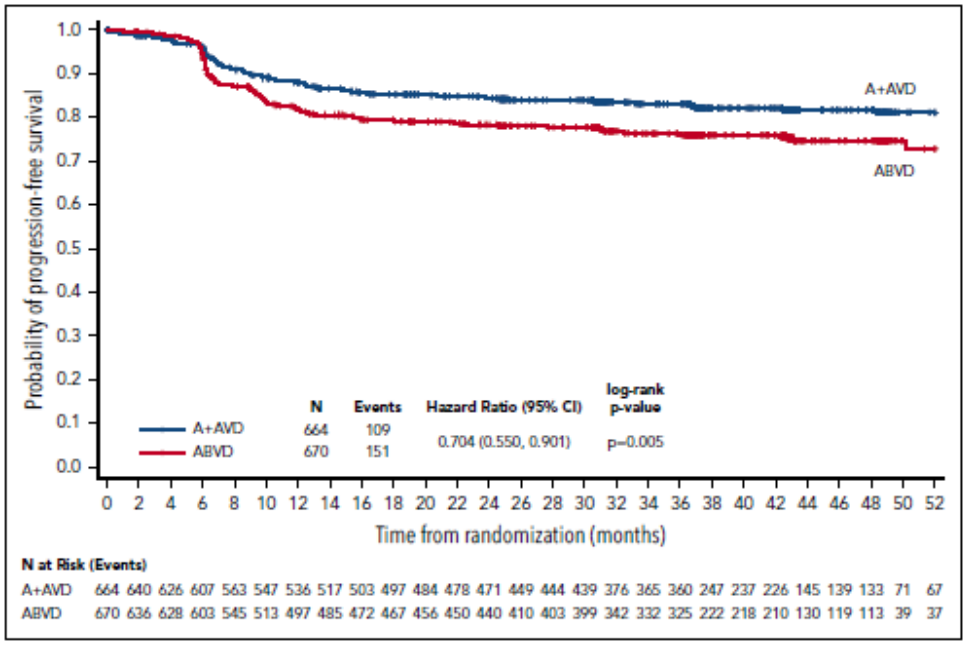
According to investigator assessment, the 2-year PFS rate was 84.2% (95% CI, 81.1 to 86.9) of BV + AVD patients and 78.0% (95% CI, 74.4 to 81.1) of ABVD patients, with stratified HR of 0.70 (95% CI, 0.54 to 0.91).

Additional Follow-up Data: Progression-free survival (PFS)

*3-year Update*

An exploratory analysis of investigator-assessed 3-year PFS in the ITT population from the ECHELON-1 trial has been published. Different from the primary outcome of mPFS in the initial publication, PFS was defined was time from randomization to first occurrence of disease progression or death from any cause. Data cut-off for this exploratory analysis was October 15, 2018, corresponding to a median follow-up of 37.1 months (range 0.0 to 66.9 months). Results showed that PFS rates were 83.1% (95% CI, 79.9 to 85.9) for the BV + AVD group compared to 76.0% (95% CI, 72.4 to 79.2) for ABVD treatment, corresponding to HR of 0.70 (95% CI, 0.55 to 0.90); the K-M curve is presented in Table 6. The p-value was 0.005, although this was nominal and not adjusted for multiplicity. Subgroup analysis of PFS based on clinical stage at baseline showed favourable results for BV + AVD in patient with Stage IV disease, with HR of 0.72 (95% CI, 0.54 to 0.97). For patients with Stage III disease, the HR point estimate favoured BV + AVD, with the upper range of the CI reaching 1.00 (HR 0.64, 95% CI, 0.41 to 1.00).[6]

## Figure 6. Kaplan-Meier Curve of PFS per Investigator, 3-year follow-up, ITT Population




*Note: BV + AVD appears as A+AVD in the figure.*

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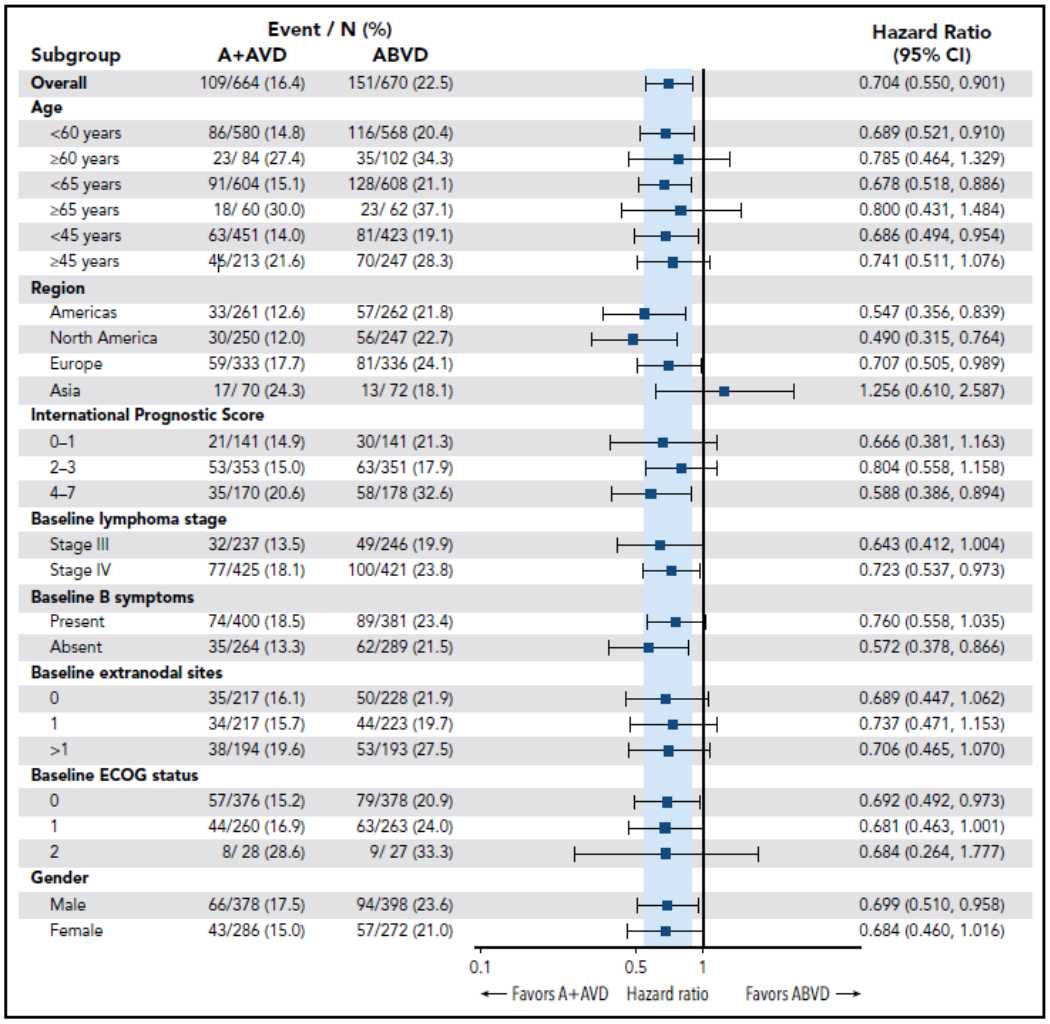
## Figure 7. PFS per Investigator Assessment in Baseline Risk Factor Subgroups, 3-year follow-up, ITT population




*Note: BV + AVD appears as A+AVD in the figure.*

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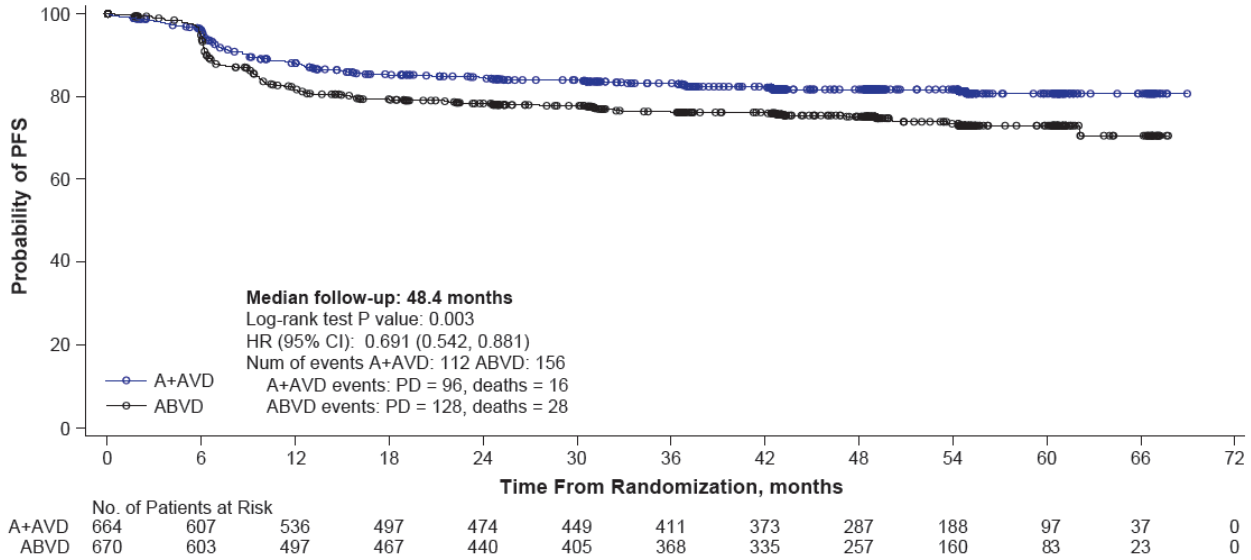
*4-year Update*

Additional post-hoc exploratory analysis of investigator-assessed 4-year PFS of patients enrolled in the ECHELON-1 trial was also available as a conference abstract and presentation. Median follow-up was 48.4 months. The PFS rate in the BV + AVD group was 81.7% (95% CI, 78.3 to 84.6) and 75.1% (95% CI, 71.4 to 78.4) in patients treated with ABVD, corresponding to HR of 0.69 (95% CI, 0.54 to 0.88). Overall survival data was not yet mature. Subgroups, including patients with Stage III, showed continued and generally consistent benefit with the ITT population.[5]

## Figure 8. Kaplan-Meier Curve of PFS per Investigator, 4-year follow-up, ITT Population

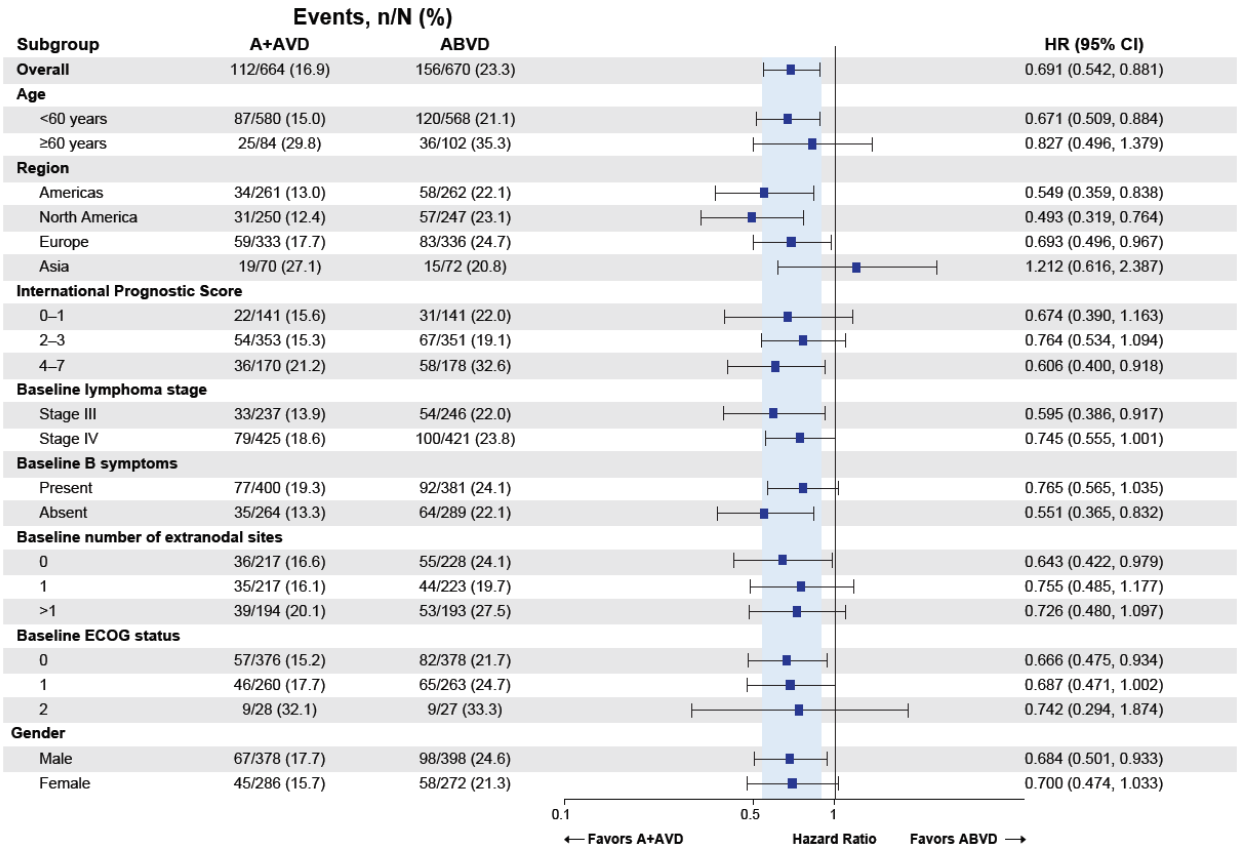



No. of Patients at Risk

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| A+AVD | 664 | 607 | 536 | 497 | 474 | 449 | 411 | 373 | 287 | 188 | 97 | 37 | 0 |
| ABVD | 670 | 603 | 497 | 467 | 440 | 405 | 368 | 335 | 257 | 160 | 83 | 23 | 0 |

*Note: BV + AVD appears as A+AVD in the figure.*
Source: pCODR Submission Materials, Seattle Genetics[3]

## Figure 9. PFS per Investigator Assessment in Baseline Risk Factor Subgroups, 4-year follow-up, ITT population




*Note: BV + AVD appears as A+AVD in the figure.*
Source: Checkpoint Meeting Document, June 2020[7]

### *Quality of Life*

Patient-reported outcomes during treatment and follow-up, measured using EORTC QLQ-C30, were considered secondary endpoints. Other assessments such as FACIT-Dyspnea 10 were used as part of exploratory analysis.

Compliance (i.e., number of forms completed out of those anticipated) was generally high across both treatment groups. For EORTC QLQ-C30, compliance rates measured from baseline, during treatment, and at EOT were similar between treatment groups, ranging between 88 to 98% in patients who received BV + AVD and 86 to 97% in those treated with ABVD. Overall, the EORTC QLQ-C30 mean summary scores over time across treatment cycles were lower in the BV + AVD group; however, during post-treatment follow-up, scores had returned to baseline levels or better. The trend in mean summary scores over time can be seen in Figure 11 below.[4] Similarly, for the global health status/QoL subscale, mean scores across treatment and at the end of treatment were lower in the BV + AVD group but had improved to at least baseline during the post-treatment follow-up period. An analysis of change in scores from baseline to EOT using linear mixed models showed that there was generally a decrease in global health status/QoL scores in the BV + AVD group and increase in scores in the ABVD group; however, the differences between the two groups were below the specified minimally important difference of 10 points and thus deemed not clinically meaningful.[8] An analysis of change in scores from baseline during treatment using linear mixed models for this subscale can be seen in Table 26. Similar patterns were seen for other subscale and symptom scores.

Results from exploratory PRO analysis, for example FACIT-Dyspnea 10 were consistent with EORTC QLQ-C30 results and showed a similar trend of unfavourable scores for the BV + AVD group compared to ABVD during the treatment period. Compliance with the FACIT-Dyspnea 10 questionnaires ranged from 86% to 98% across treatment groups, and similarly, compliance with the FACT/GOG-NTx questionnaire ranged from 85% to 98%.[4]

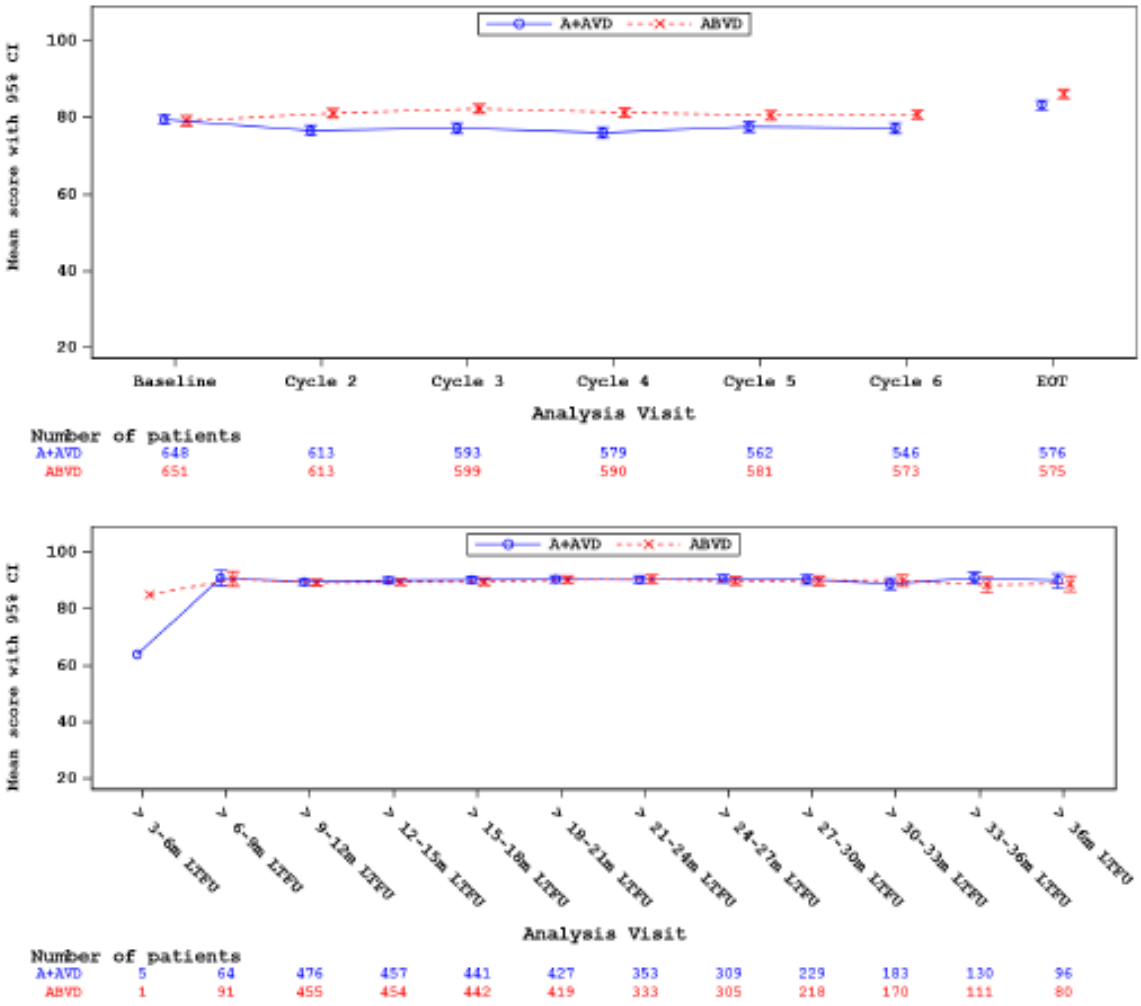
[redacted].[8] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Results from the FACT/GOG-Ntx neurotoxicity subscale scores showed greater symptoms of neuropathy in patients treated with BV +AVD, consistent with the observed pattern of adverse effects. Through the course of treatment, mean subscale scores were lower (indicating worse QoL) in the BV + AVD group compared to those in the ABVD group, and a difference favouring ABVD was seen from Cycle 2 to 6. The difference in the neurotoxicity subscale scores at Cycle 4, 5 and 6 were clinically meaningful, using 3 points as the threshold for minimal important difference.[3]

Compliance with the EQ-5D-3L was also high, ranging from 87% to 99% across treatment groups. No difference in the mean scores between the two treatment groups was seen, when compared using a minimal important difference of 0.07 (as established for the UK time trade-off score). Mean scores returned to baseline after treatment. The trends observed were consistent between the UK-based and US-based value sets.[4]

Overall, aside from results from the exploratory FACT/GOG-Ntx analysis, data from patient-reported outcomes did not show a clinically meaningful difference between BV + AVD and ABVD, though there was a trend of unfavourable scores observed in the BV + AVD group during the treatment period. This is of potential concern, suggesting that BV + AVD may lead to experiencing a lower quality of life and function, as well as symptoms such as dyspnea and fatigue; however, such concerns seem to be limited to the treatment period, without long-term effects. This is consistent with the higher frequency of severe TEAEs (≥ Grade 3) and serious adverse events observed in patients who received BV + AVD.

## Figure 10. EORTC-QLQ-C30 Mean Summary Scores Over Time, During Treatment and Long-Term Follow-Up Visits (LTFU), ITT Population




*Note: BV + AVD appears as A+AVD in the figure.*
Source: EPAR 2018, p.65[4]

## Table 26: Change in EORTC QLQ-C30 Global Health Status/QoL Summary Scores from Baseline, Linear Mixed Models, ITT

| | BV + AVD (n=664) | | ABVD (n=670) | | BV + AVD vs. ABVD | |
|---|---|---|---|---|---|---|
| | N | LS Mean (SE) | N | LS Mean (SE) | LS Mean Difference (SE) | 95% CI for LS Mean Difference |
| Baseline | 648 | 63.839 (0.9983) | 651 | 62.363 (0.9938) | 1.476 (1.2112) | (-0.901 to 3.852) |
| Change from baseline to | | | | | | |
| Cycle 2 | 609 | -1.989 (0.8571) | 609 | 3.104 (0.7728) | -5.094 (1.0380) | (-7.130 to -3.057) |
| Cycle 3 | 584 | -2.005 (0.8695) | 596 | 3.985 (0.7402) | -5.990 (1.0295) | (-8.010 to -3.970) |
| Cycle 4 | 573 | -3.085 (0.8545) | 584 | 2.537 (0.7865) | -5.621 (1.0450) | (-7.672 to -3.571) |
| Cycle 5 | 559 | -2.417 (0.8772) | 578 | 1.610 (0.7920) | -4.027 (1.0713) | (-6.128 to -1.925) |
| Cycle 6 | 537 | -3.374 (0.8552) | 570 | 1.127 (0.8043) | -4.501 (1.0606) | (-6.582 to -2.420) |

*ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine; BV + AVD = brentuximab vedotin plus doxorubicin, vinblastine, dacarbazine; CI = confidence interval; LS=Least Square; SE=Standard Error*
*Source: adapted from Clinical Study Report, Table 15.2.19.4, p.6248 - 6250*[8]

***Harms Outcomes***

Treatment-Emergent Adverse Events (TEAEs)

TEAEs were evaluated in the safety population, comprised of 662 patients in the BV + AVD group and 659 patients in the ABVD group.[2]

TEAEs were reported in 653 (99%) and 646 (98%) of patients in the BV + AVD and ABVD groups, respectively. Severe TEAEs of Grade ≥3 occurred in 549 (83%) of patients in the BV + AVD group and 434 (66%) of patients in the ABVD group. Serious TEAEs were recorded in 284 patients (43%) treated with BV + AVD and 128 patients (27%) treated with ABVD. Hospitalizations also occurred in 242 patients (37%) who received BV + AVD, and 186 patients (28%) who received ABVD.[2] Of the reasons for hospitalization, toxicity or an adverse event were most common and higher in the BV + AVD group (76% vs. 71% of BV + AVD and ABVD, respectively) reflecting the higher frequency of serious TEAEs and ≥ Grade 3 TEAEs seen in the BV + AVD group.[8]

Most common TEAEs, reported in at least 10% of patients in either group, are show in Table 27. Notably, the following TEAEs of any grade were reported in a greater number of patients treated with BV + AVD compared to ABVD: neutropenia (58% vs. 45%), febrile neutropenia (19% vs. 8%), diarrhea (27% vs. 18%), weight loss (22% vs. 6%), abdominal pain (21% vs. 10%), and anemia (21% vs. 10%). Various TEAEs associated with peripheral neuropathy were common in both groups, but overall occurred more frequently in patients randomized to BV + AVD; any peripheral neuropathic event (SMQ), including peripheral sensory neuropathy, peripheral motor neuropathy, and related adverse events occurred in 67% vs. 43% of patients in the BV + AVD and ABVD groups, respectively.[2] Although fertility was not part of the formal assessment in this trial, similar number of pregnancies were observed in each treatment group suggesting no difference in effect. At data cut-off, secondary malignancies were reported in 1.5% of patients (n=10) receiving BV + AVD and 2.1% of patients (n=14) receiving ABVD.[4]

Infusion-related reactions of any grade were reported in 9% (n=57) and 15% (n=100) of patients receiving BV + AVD and ABVD, respectively. At least one Grade 3 infusion-related reaction was experienced by <1% (n=3) of patients in the BV + AVD group and 1% (n=7) patients in the ABVD group. A dose modification due to infusion-related reactions was required in 2% (n=13) and 5% (n=35) of patients administered BV + AVD and ABVD, respectively. None of the patients experienced anaphylaxis.[4]

Discontinuation of one or more drug components of the combination due to an TEAE occurred in 88 patients (13%) in the BV + AVD group, compared to 105 patients (16%) in the ABVD group.[2,49] The most frequently reported TEAE leading to premature discontinuation of one or more components of BV + AVD (in at least two patients) were peripheral sensory neuropathy (3%),

peripheral neuropathy (2%), peripheral motor neuropathy (2%), and febrile neutropenia (1%). For patients treated with ABVD, the most frequently reported TEAE resulting in premature discontinuation of one or more components of the drug combination (in at least two patients) were dyspnea (4%), pulmonary toxicity (2%), cough (2%), reduced carbon monoxide diffusing capacity (2%), and pneumonitis (1%). Discontinuation of the entire treatment combination due to an adverse event occurred in 4% (24 of 664 patients) treated with BV + AVD and 3% (22 of 670 patients) in the ABVD group.[4,49]

Dose modifications, defined as a dose reduction, delay, or hold in any of the assigned regimen, occurred more often in the BV + AVD group. TEAEs resulted in a dose modification in greater proportion of patients who received BV + AVD, required in 64% (n=423) and 44% (n=293) of patients in the BV + AVD and ABVD groups, respectively, with neutropenia most frequently being the cause of dose modification in both treatment groups. Specifically, a dose delay was the most frequently reported modification on both groups, seen in 48% of patients (n=318) who received BV + AVD and 33% of patients (n=217) who received ABVD; a dose reduction was required due to an AE in 29% of patients (n=191) treated with BV + AVD and 10% (n=65) treated with ABVD.

## Table 27: Summary of Adverse Events, Safety Population – Including TEAEs Reported in ≥ 10% of Patients in Either Treatment Group

| Safety summary — no. (%) | A+AVD N = 662 | | ABVD N = 659 | |
|---|---|---|---|---|
| Any adverse event | 653 (99) | | 646 (98) | |
| Drug-related adverse event | 641 (97) | | 617 (94) | |
| Grade ≥3 adverse event | 549 (83) | | 434 (66) | |
| Drug-related Grade ≥3 adverse event | 525 (79) | | 389 (59) | |
| Serious adverse event | 284 (43) | | 178 (27) | |
| Drug-related serious adverse event | 240 (36) | | 125 (19) | |
| Adverse event resulting in drug discontinuation | 88 (13) | | 105 (16) | |
| Adverse event resulting in dose modification | 423 (64) | | 293 (44) | |
| Dose held | 44 (7) | | 32 (5) | |
| Dose interrupted | 22 (3) | | 33 (5) | |
| Dose reduced | 191 (29) | | 65 (10) | |
| Dose delayed | 318 (48) | | 217 (33) | |
| Death during treatment* | 9 (1) | | 13 (2) | |
| Death due to drug-related adverse events | 8 (1) | | 7 (1) | |
| Hospitalizations | 242 (37) | | 186 (28) | |
| **Common adverse events — no. (%)** | **Any grade** | **Grade ≥3** | **Any grade** | **Grade ≥3** |
| Neutropenia | 382 (58) | 357 (54) | 295 (45) | 260 (39) |
| Nausea | 348 (53) | 20 (3) | 371 (56) | 7 (1) |
| Constipation | 279 (42) | 11 (2) | 241 (37) | 4 (<1) |
| Vomiting | 216 (33) | 23 (3) | 183 (28) | 9 (1) |
| Fatigue | 211 (32) | 19 (3) | 211 (32) | 7 (1) |
| Peripheral sensory neuropathy | 189 (29) | 31 (5) | 111 (17) | 3 (<1) |
| Diarrhea | 181 (27) | 19 (3) | 121 (18) | 5 (<1) |
| Pyrexia | 179 (27) | 19 (3) | 147 (22) | 13 (2) |
| Peripheral neuropathy | 174 (26) | 27 (4) | 85 (13) | 6 (<1) |
| Alopecia | 173 (26) | 1 (<1) | 146 (22) | 0 |
| Weight decreased | 148 (22) | 6 (<1) | 40 (6) | 1 (<1) |
| Abdominal pain | 142 (21) | 21 (3) | 65 (10) | 4 (<1) |
| Anemia | 140 (21) | 54 (8) | 67 (10) | 25 (4) |
| Stomatitis | 138 (21) | 10 (2) | 104 (16) | 3 (<1) |
| Febrile neutropenia | 128 (19) | 128 (19) | 52 (8) | 52 (8) |
| Bone pain | 126 (19) | 6 (<1) | 66 (10) | 1 (<1) |
| Insomnia | 126 (19) | 4 (<1) | 82 (12) | 1 (<1) |
| Decreased appetite | 118 (18) | 5 (<1) | 76 (12) | 2 (<1) |
| Cough | 97 (15) | 0 | 123 (19) | 0 |
| Headache | 95 (14) | 2 (<1) | 94 (14) | 2 (<1) |
| Arthralgia | 89 (13) | 2 (<1) | 78 (12) | 0 |
| Neutrophil count decreased | 86 (13) | 83 (13) | 79 (12) | 67 (10) |
| Dyspepsia | 84 (13) | 1 (<1) | 75 (11) | 0 |
| Paresthesia | 84 (13) | 0 | 73 (11) | 0 |
| Back pain | 83 (13) | 4 (<1) | 49 (7) | 0 |
| Dyspnea | 82 (12) | 9 (1) | 124 (19) | 11 (2) |
| Myalgia | 81 (12) | 3 (<1) | 71 (11) | 3 (<1) |
| Pain in extremity | 81 (12) | 2 (<1) | 67 (10) | 1 (<1) |
| Oropharyngeal pain | 72 (11) | 2 (<1) | 55 (8) | 3 (<1) |
| Upper respiratory tract infection | 70 (11) | 5 (<1) | 70 (11) | 3 (<1) |
| Alanine aminotransferase increased | 68 (10) | 22 (3) | 26 (4) | 1 (<1) |
| **G-CSF primary prophylaxis — no. (%)** | **No (n = 579)** | **Yes (n = 83)** | **No (n = 616)** | **Yes (n = 43)** |
| Febrile neutropenia in Cycle 1 | 61 (11) | 1 (1) | 24 (4) | 2 (5) |
| Febrile neutropenia during treatment | 119 (21) | 9 (11) | 49 (8) | 3 (7) |
| Any neutropenia† | 425 (73) | 29 (35) | 352 (57) | 9 (21) |
| Neutropenia Grade ≥3† | 406 (70) | 24 (29) | 309 (50) | 8 (19) |
| Grade ≥3 adverse event | 502 (87) | 47 (57) | 414 (67) | 20 (47) |
| Infections and infestations (SOC) | 322 (56) | 39 (47) | 312 (51) | 19 (44) |
| Grade ≥3 infections and infestations (SOC) | 107 (18) | 9 (11) | 63 (10) | 3 (7) |
| Serious adverse event | 257 (44) | 27 (33) | 171 (28) | 7 (16) |
| Serious adverse events of febrile neutropenia, neutropenia, sepsis, neutropenic sepsis, pyrexia, or infections and infestations (SOC) | 190 (33) | 20 (24) | 107 (17) | 4 (9) |
| Death during treatment* | 8 (1) | 1 (1)‡ | 12 (2) | 1 (2) |

*Defined as a death that occurred within 30 days after the last dose of frontline therapy.
†Neutropenia and neutropenia Grade ≥3 (neutrophil count <1000 per cubic millimeter) include the preferred terms of 'neutropenia' and 'neutrophil count decreased'.
‡The patient in the A+AVD group who had G-CSF primary prophylaxis received G-CSF for treatment of neutropenia, which occurred before day 5.
A+AVD, brentuximab vedotin plus doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; G-CSF, granulocyte colony-stimulating factor; SOC, system organ class for the noted event.

*Note: BV + AVD appears as A+AVD in the table.*
Source: From the New England Journal of Medicine, Connors JM et al., Brentuximab vedotin with chemotherapy for stage III or IV Hodgkin's lymphoma, 378, 331-344. Copyright ©2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[2]

TEAEs of Interest: neutropenia, febrile neutropenia, infections, peripheral neuropathy, pulmonary toxicity

Neutropenia of any grade was reported in 58% of patients (382 of 662 patients) treated with BV + AVD and 45% of patients (295 of 659) treated with ABVD; febrile neutropenia was reported in 19% of patients (n=128) in BV + AVD and 8% of patients (n=52) in ABVD treatment group. For both treatment groups, febrile neutropenia was reported more frequently in patients ≥60 years of age. In this older group, neutropenia was reported in 37% (31 of 84 patients) and 17% (17 of 102) in the BV + AVD and ABVD groups, respectively, whereas those younger than 60 years had an incidence of 17% (97 of 580 patients) and 6% (35 of 568) in the BV + AVD and ABVD groups, respectively. Furthermore, febrile neutropenia was reported more often in earlier cycles of treatment in both groups (BV + AVD: 9% in Cycle 1 vs. 1-6% in Cycles 2-6; ABVD: 4% in Cycle 1 vs. ≤ 1% in Cycles 2-6). In both groups, 1% or fewer patients discontinued a trial drug due to neutropenia or febrile neutropenia.[2]

A higher rate of infections was reported in the BV + AVD group, prior to implementing G-CSF prophylaxis. Initially, infections (of any grade) were reported in 55% of patients (n=361) in the BV + AVD group and 50% (n=331) in the ABVD group; infections of ≥ Grade 3 were reported in 18% of patients (n=116) treated with BV + AVD and 10% (n=66) treated with ABVD.[2] After implementation of G-CSF primary prophylaxis, the incidence of febrile neutropenia and infections overall decreased, although remained higher in the BV + AVD group compared to ABVD, as shown in Table 27 above.

Peripheral neuropathy (of all grades) was reported in 67% of patients (442 of 662) in the BV + AVD group compared to 43% of patients (286 of 659) in the ABVD group; peripheral neuropathy of ≥Grade 3 occurred in 11% of patients (n=70) treated with BV + AVD and 2% of patients (n=11) treated with ABVD. Of those who experienced peripheral neuropathy, 10% (44 of 442) in the BV + AVD group and 4% (11 of 286) in the ABVD group discontinued a trial drug.[2] Onset of peripheral neuropathy was reported at a median of 8 weeks (range 0 to 29 weeks) in patients treated with BV + AVD and 7 weeks (range 0 to 32 weeks) for those treatment with ABVD. Of patients who were treated with BV + AVD and experienced peripheral neuropathy, 51% had resolution or improvement of symptoms by end of treatment, which increased to 67% at the time of last follow-up.[4] Specifically, at the time of the last follow-up visit, 43% of patients (191 of 442) treated with BV + AVD who had developed peripheral neuropathy experienced resolution, and 24% of patients (104 of 442) experienced an improvement by at least one grade. In patients who received BV + AVD, at the time of the final follow-up, most ongoing peripheral neuropathy were Grade 1 (64%) or Grade 2 (29%) in severity.[2]

Pulmonary-related toxicity (i.e., related to interstitial lung disease) of any grade occurred in 2% of patients (12 of 662) receiving BV + 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 + AVD, whereas pneumonitis, pulmonary toxicity and interstitial lung disease were reported most frequently in patients treated with ABVD.[4] Grade 3 or higher pulmonary toxicity was reported in <1% (n=5) and 3% (n=21) of patients in the BV + AVD and ABVD groups, respectively.[2] Similarly, interstitial lung disease reported as a SAE was seen in <1% of BV + AVD and 3% of ABVD patients. The most commonly reported serious TEAE in the ABVD group was pneumonitis (n=12, 2%) and pulmonary toxicity (n=5, <1%).[4] Incidence of pulmonary-related toxicity was also higher in older patients who received ABVD, but no age correlation was seen in the BV + AVD group.[4]

Drug-Related AEs

Adverse events of any grade deemed related to treatment occurred in a high number of patients (97%, n=641 BV + AVD vs. 94%, n=617 ABVD). Severe AEs ≥ Grade 3 thought to be drug-related occurred in 79% (525 of 662) patients in the BV + AVD group and 59% (389 of 659) in the ABVD group. Furthermore, one or more drug-related SAE was reported in 36% of patients (n=240) receiving BV + AVD and 19% of patients (n=125) receiving ABVD. In the BV + AVD group, the most drug-related SAEs (reported in at least five patients) included febrile neutropenia (17%), pyrexia (6%), neutropenia (3%), pneumonia (2%), abdominal pain (2%), and sepsis (2%). In patients who received ABVD, the most frequently reported drug-related SAEs included febrile neutropenia (6%), pyrexia (3%), and pneumonitis (2%).[4]

Hepatotoxicity, thrombocytopenia, anemia, and hyperglycemia of any grade were all also reported at a higher incidence in patients treated with BV + AVD compared to ABVD. For hepatotoxicity, 11% of patients (n=76) in the BV + AVD group and 5% of patients (n=32) in the ABVD group reported abnormal liver-related investigations that were deemed drug-related. Anemia secondary to treatment was reported in 17% (n=112) of those in the BV + AVD group compared to 8% (n=53) in the ABVD group, and

thrombocytopenia was reported in 4% (n=28) vs. 2% (n=13) of patients treated with BV + AVD and ABVD, respectively. Drug-related hyperglycemia was also reported in 18% of patients (n=116) treated with BV + AVD compared to 5% (n=34) treated with ABVD.[4]

TEAE According to Clinical Stage at Baseline

In patients with Stage III disease, a similar proportion of TEAEs, including those deemed drug-related, were reported in both treatment groups (Table 28). However, like the overall population, higher incidence of ≥ Grade 3 TEAEs and serious TEAEs were reported in patients treated with BV + AVD. The most commonly reported ≥ Grade 3 TEAEs (in at least 10% of patients in either group) included neutropenia (50%, 117 of 236 patients in BV + AVD; 37%, 91 of 244 in ABVD) and febrile neutropenia (20%, 48 of 236 patients in A+ABD; 7%, 17 of 244 in ABVD). The most commonly reported serious TEAEs in patients with Stage III disease (reported for at least five patients in either group) were febrile neutropenia (18% BV + AVD vs. 6% ABVD) and pyrexia (7% BV + AVD vs. 3% ABVD).[4]

Patients who had Stage IV disease at baseline also experienced similar proportion of TEAEs and drug-related AEs between the two treatment groups. Similar to patients with Stage III disease and the overall population, there was higher incidence of ≥ Grade 3 TEAEs and serious TEAEs noted in the BV + AVD group (Table 29). Of the safety population with Stage IV disease who experienced a ≥ Grade 3 TEAE (reported in at least 10% in each group), neutropenia was also most common (56%, 239 of 424 patients in BV + AVD; 41%, 169 of 413 in ABVD), followed by febrile neutropenia (19%, 80 of 424 patients in BV + AVD; 8%, 35 of 413 in ABVD). Similar to patients with Stage III disease, febrile neutropenia (17% BV + AVD vs. 7% ABVD) and pyrexia (6% BV + AVD vs. 5% ABVD) were also the most frequent serious TEAEs (reported in at least five patients in either group).[4] Notably, in the BV + AVD treatment group, patients with Stage IV disease had lower incidence of serious TEAE, drug-related SAE, and AE resulting in study drug discontinuation compared to those with baseline Stage III cHL:

- Serious adverse event
  - BV + AVD:  Stage III = 48% (113 of 236); Stage IV = 40% (170 of 424)
  - ABVD: Stage III = 26% (63 of 244); Stage IV = 28% (114 of 413)
- Drug-related serious adverse event
  - BV + AVD: Stage III = 42% (99 of 236); Stage IV = 33% (140 of 424)
  - ABVD: Stage III = 17% (42 of 244); Stage IV = 20% (83 of 413)
- Adverse events resulting in a study drug discontinuation
  - BV + AVD: Stage III = 19% (44 of 236); Stage IV = 10% (44 of 424)
  - ABVD: Stage III = 16% (39 of 244); Stage IV = 16% (66 of 413)[4]

## Table 28: Overview of Safety in Patients with Baseline Stage III cHL Safety Population

| | A+AVD N=236 n (%) | ABVD N=244 n (%) |
|---|---|---|
| Any AE | 235 (100) | 241 (99) |
| Treatment-related AE | 231 (98) | 232 (95) |
| Grade 3 or higher AE | 196 (83) | 155 (64) |
| Treatment-related Grade 3 or higher AE | 188 (80) | 139 (57) |
| SAE | 113 (48) | 63 (26) |
| Treatment-related SAE | 99 (42) | 42 (17) |
| AEs resulting in study drug discontinuation | 44 (19) | 39 (16) |
| AE resulting in dose modification | 155 (66) | 109 (45) |
| Dose held | 18 (8) | 10 (4) |
| Dose interrupted | 10 (4) | 13 (5) |
| Dose reduced | 70 (30) | 24 (10) |
| Dose delayed | 114 (48) | 79 (32) |
| On-study deaths | 4 (2) | 5 (2) |
| Deaths due to study treatment-related AEs | 3 (1) | 2 (<1) |

Source: 0114\mpi\0068\ICR_BIO\dev\primary\programs\tables\ADt15.3.1.1E-teae_stagiii.sas, run date 29 May 2018: 11:53.
TEAEs were defined as any AE that occurred after administration of the first dose of study drug and through 30 days after the last dose of frontline therapy.
A patient was counted once for each type of event.
AEs were coded using the MedDRA dictionary Version 19.0.
A+AVD=brentuximab vedotin (Adcetris) plus doxorubicin (Adriamycin), vinblastine, dacarbazine, ABVD=doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine, AE=adverse event, MedDRA=Medical Dictionary for Regulatory Activities, PTFU=posttreatment follow-up, TEAE=treatment-emergent adverse event.
(a) On-study deaths were defined as deaths that occurred within 30 days of the last dose of frontline therapy.
(b) PTFU deaths were defined as deaths that occurred after 30 days of the last dose of frontline therapy.

*Note: BV + AVD appears as A+AVD in the table*
Source: EPAR 2018, p.96[4].

## Table 29: Overview of Safety in Patients with Baseline Stage IV cHL Safety Population

| | A+AVD N=424 n (%) | ABVD N=413 n (%) |
|---|---|---|
| Any adverse event | 416 (98) | 403 (98) |
| Drug-related adverse event | 408 (96) | 383 (93) |
| Grade 3 or higher adverse event | 352 (83) | 278 (67) |
| Drug-related Grade 3 or higher adverse event | 336 (79) | 250 (61) |
| Serious adverse event | 170 (40) | 114 (28) |
| Drug-related serious adverse event | 140 (33) | 83 (20) |
| Adverse events resulting in study drug or dose discontinuation | 44 (10) | 66 (16) |
| Adverse event resulting in dose modification | 268 (63) | 184 (45) |
| Dose held | 26 (6) | 22 (5) |
| Dose interrupted | 12 (3) | 20 (5) |
| Dose reduced | 121 (29) | 41 (10) |
| Dose delayed | 204 (48) | 138 (33) |
| On-study deaths | 5 (1) | 8 (2) |
| Deaths due to drug-related adverse events | 5 (1) | 5 (1) |

Source: m2.7.4 – ECHELON-1, Table 4.a.

*Note: BV + AVD appears as A+AVD in the table.*
Source: EPAR 2018, p.96[4]

Deaths

At the time of data cut-off, there were a total of 67 deaths. In the BV + AVD treatment group, 9 deaths occurred during treatment and 19 occurred during post-treatment follow-up; in the ABVD group, 13 patients died during treatment, whereas 26 died during post-treatment follow-up.[2,4]

During the on-study treatment phase (within 30 days after last dose of frontline therapy), 8 of the 9 deaths in the BV + AVD group was deemed to be due to a drug-related AE. Of the treatment-related deaths, 7 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. Another two patients died during the post-treatment follow-up period but within 120 days of the last dose of treatment, with the cause of death deemed related to a treatment-emergent SAE experienced during treatment. All of the patients who died during treatment with BV + AVD received the randomized regimen only.[4]

In the ABVD group, 7 out of the 13 on-study deaths were deemed to be drug-related, with the majority being due to pulmonary-related toxicity. The death of four more patients, which occurred during the post-treatment follow-up period but within 120 days of the last dose of treatment, were also deemed to be due to SAEs experienced during frontline treatment. One patient who died during study treatment had switched from the randomly assigned regimen to an alternative frontline treatment after assessment with Cycle 2 PET.[4]

*Additional Follow-up Data*

*3-year Update*

Select safety information was included in the 3-year follow-up data publication, namely resolution of peripheral neuropathy. Of the patients who developed peripheral neuropathy, 62% (272 of 442) in the BV + AVD group had complete resolution, compared to 73% (209 of 286) in the ABVD group. Furthermore, 17% (73 of 442) of patients treated with BV + AVD group and 9% (27 of 286) treated with ABVD had improvement in symptoms. Of patients who had ongoing peripheral neuropathy, most were either Grade 1 or 2 in severity in both treatment groups. Development of secondary malignancies were noted in 34 patients; 14 patients (2.3%) in the BV + AVD group and 20 patients (3%) in the ABVD group.[6]

*4-year Update*

Safety information from the 4-year follow-up data showed that of patients who developed peripheral neuropathy, 68% (300 of 442) in the BV + AVD group had complete resolution compared to 76% (217 of 286) in the ABVD group. Improvement in symptoms (by at least 1 grade) were seen in 15% (65 of 442) and 8% (23 of 286) of patients in the BV + AVD and ABVD groups, respectively. Of patients experiencing residual peripheral neuropathy (n=142 in BV + AVD; n=69 in ABVD), most continued to be either Grade 1 or 2 in severity. The median time for complete resolution of peripheral neuropathy was 30 weeks (range 0 to 262) compared to 15 weeks (0 to 234) in patients treated with BV + AVD and ABVD, respectively. In patients who did not experience complete resolution, improvement in symptoms were seen at median of 41 weeks (range 8 to 205) in the BV + AVD group and 12 weeks (range 2 to 70) in the ABVD group.[5]

## 6.4 Ongoing Trials

Two ongoing trials were identified as relevant to this review and may provide future insights on using BV in combination with AVD in pediatric patients or as part of PET-response adapted therapy. The first study (NCT02979522), is an open-label single-group Phase I/II trial in pediatric patients 5 to 17 years of age with advanced stage, previously untreated cHL The COBRA study is an open-label, single group, Phase II trial that explores the PET-guided treatment approach using BV in combination with AVD for the treatment of adults with advanced stage, treatment-naïve cHL

### Table 30: Ongoing Trials of Brentuximab Vedotin in Hodgkin Lymphoma

| Trial Design | Inclusion Criteria | Intervention and Comparator | Trial Outcomes |
|---|---|---|---|
| **Study:**<br>NCT02979522[26]<br><br>**Characteristics:**<br>Open-label, single-group, Phase I/II trial<br><br>**Estimated enrolment:**<br>N = 59<br>(Phase I: up to 12 patients; Phase II: up to 59 patients including Phase I participants)<br><br>**Number of centres and number of countries:**<br>25 sites across 7 countries (Brazil, Hong Kong, Italy, Japan, Singapore, Taiwan, United States)<br><br>**Patient Enrolment Dates:**<br>September 7, 2017 (recruitment ongoing for Phase II)<br><br>**Estimated primary completion date:**<br>June 30, 2020 | **Key Inclusion Criteria:**<br>• Pediatric patients (5 to 17 years)<br>• Newly diagnosed histologically confirmed CD30+ classical HL<br>• Advanced stage (Stage III and IV disease).<br>• Treatment-naive<br>• Lansky Play-performance or Karnofsky Performance Status scores of ≥ 50<br><br>**Key Exclusion Criteria:**<br>• Nodular lymphocyte predominant HL<br>• Known active cerebral/meningeal disease, including signs or symptoms of PML or history of PML<br>• Sensory or motor peripheral neuropathy.<br>• Symptomatic neurologic disease requiring medication, or which compromises normal ADLs | **Phase I:**<br>Combination of:<br>Brentuximab vedotin 48 mg/m$^2$ IV<br>OR<br>Brentuximab vedotin 36 mg/m$^2$ IV<br><br>PLUS<br>Doxorubicin 25 mg/m$^2$ IV<br>Vinblastine 6 mg/m$^2$ IV<br>Dacarbazine 375 mg/m$^2$ IV<br><br>Administered as infusions on Day 1 and 15 of each 28-day cycle.<br><br>Maximum of 6 cycles.<br><br>**Phase II:**<br>Same combination will be used, except dose of brentuximab will be according to what is established in Phase I, based on tolerability. | Primary:<br>**Phase I**<br>• Recommended dose of brentuximab vedotin<br>• AEs, SAEs<br>**Phase II**<br>• CR<br>• PET negativity after 2 Cycles<br>• PR<br>• OR<br>• % able to complete 6 Cycles of protocol treatment at recommended dose<br><br>Secondary:<br>**Phase II**<br>• PFS<br>• EFS<br>• OS<br>• DOR<br>• % receiving RT for HL following study treatment<br>• AEs, SAE<br>• % ATA positive; persistently positive or transiently positive, and nATA positive<br>• PK (mean Cmax, AUC, median Tmax)<br>• Peripheral neuropathy; incidence, time to onset, resolution<br>• Immune reconstitution over time (peripheral blood CD34+ count; enumeration of total |

| Trial Design | Inclusion Criteria | Intervention and Comparator | Trial Outcomes |
|---|---|---|---|
| **Estimated study completion:** September 24, 2021<br><br>**Funding** Millennium Pharmaceuticals, Inc. (Takeda) | | | lymphocyte count and lymphocyte subsets; total Ig and IgG, IgM, IgA levels; levels of antibodies to tetanus, HiB, and polio serotypes)<br>• ATA Titer and associated PK properties, CR rate, AEs based in patients who are ATA positive vs. negative |
| **Study:** NCT03517137[25] COBRA study<br><br>**Characteristics:** Open-label, single-group, Phase II<br><br>**Estimated enrolment:** N=150 (ongoing recruitment)<br><br>**Number of centres and number of countries:** 22 sites in 9 countries (Belgium, Croatia, Denmark, Egypt, Netherlands, Poland, Portugal, Slovakia, Spain,<br><br>**Patient Enrolment Dates:** August 1, 2019 (ongoing recruitment)<br><br>**Estimated primary completion date:** March 1, 2021<br><br>**Estimated study completion:** September 1, 2023<br><br>**Funding:** European | **Key Inclusion Criteria:**<br>• Adults 18 to 60 years<br>• Histologically proven classical HL<br>• Treatment-naïve<br>• Clinical Stages:<br>○ Stage IIB with large mediastinal mass > 1/3 max transverse diameter thorax and/or extranodal lesion(s)<br>○ Stage III - IV<br><br>**Key Exclusion Criteria:**<br>• Cerebral or meningeal disease, including signs or symptoms of PML<br>• Symptomatic neurologic disease requiring medications or compromising normal ADLs<br>• ≥ Grade 2 sensory or motor peripheral neuropathy<br>• CV conditions or values < 6 months before registration:<br>○ LVEF < 50%<br>○ NYHA Class III or IV HF<br>○ Uncontrolled CV conditions, (e.g., cardiac arrhythmias, CHF, angina, ECG evidence of acute ischemia or conduction system abnormalities)<br>○ Symptomatic CHD (stable angina pectoris allowed)<br>○ Severe uncontrolled HTN < 2 years before registration<br>○ MI<br>• Poorly controlled DM (HbA1c > 7.5% or FBG > 200 mg/dL) | <u>Initial: BrAVD x 1 cycle</u><br>Brentuximab vedotin 1.2 mg/kg IV<br>Doxorubicin 25 mg/m² IV<br>Vinblastine 6mg/m² IV<br>Dacarbazine mg/m² IV<br><br>Administered as infusions on Day 1 and 15, for one 28-day cycle (4 weeks).<br><br><u>PET-response adapted treatment thereafter:</u><br><br><u>PET-negative (DS 1 to 3)</u><br>BrAVD x 5 cycles<br>Brentuximab vedotin 1.2 mg/kg IV<br>Doxorubicin 25 mg/m² IV<br>Vinblastine 6mg/m² IV<br>Dacarbazine mg/m² IV<br><br>Administered as infusions on Day 1 and 15 of 28-day cycles, for 5 cycles.<br><br><u>PET-positive (DS 4 to 5)</u><br>BrECADD x 6 cycles<br>Brentuximab vedotin 1.8 mg/kg (Day 1)<br>Etoposide 150 mg/m² (Days 2,3,4)<br>Cyclophosphamide 1250 mg/m² (Day 2)<br>Doxorubicin 40 mg/m² (Day 2)<br>Dacarbazine 250 mg/m² (Days 3,4)<br><br>Administered as IV infusions on specified days in 21-day cycles for, 6 cycles. | <u>Primary:</u><br>• mPFS*<br><br><u>Secondary:</u><br>• Proportion of patients with a negative FDG-PET taken at the end of their first cycle of BrAVD.<br>• PFS<br>• OS<br>• AEs |

| Trial Design | Inclusion Criteria | Intervention and Comparator | Trial Outcomes |
|---|---|---|---|
| Organisation for Research and Treatment of Cancer - EORTC | • Active systemic viral, bacterial, or fungal infection requiring systemic antibiotics < 2 weeks prior to registration<br>• Concomitant or previous malignancies within past 5 years (except adequately treated carcinoma in situ of the cervix, nonmelanoma skin cancer)<br>• Previous treatment with anti CD30 antibodies | At completion of chemotherapy, consolidation RT offered to patients with DS 4 or 5. | |

*ADL = activities of daily living; AE = adverse event; ATA = antitherapeutic antibody; AUC = Area Under the Plasma Concentration-Time Curve; CHD = coronary heart disease; CHF = congestive heart failure; Cmax = mean maximum observed plasma concentration; CR = complete remission; CV = cardiovascular; DM = diabetes mellitus; DOR = duration of response; DS = Deauville Score; ECG = electrocardiogram; EFS = event-free survival; FBG = fasting blood glucose; HiB = haemophilus influenza type B; HF = heart failure; HL = Hodgkin lymphoma; HTN = hypertension; Ig = immunoglobulin; IV = intravenous; LVEF = left ventricular ejection fraction; MI = myocardial infarction; mPFS = modified progression-free survival; nATA= Neutralizing Antitherapeutic Antibody; NYHA = New York Heart Association; PML = progressive multifocal leukoencephalopathy; OR = overall response; OS = overall survival; PFS = progression-free survival; PR = partial remission; REP = response-evaluable population; RT = radiotherapy; SAE = serious adverse event; TEAE = treatment emergent adverse event; Tmax = time to reach Cmax*

** mPFS is defined as the time between starting treatment and first of: 1) progressive disease; 2) start of new treatment of classical HL when not in complete response at end of protocol treatment; 3) death due to any cause*

# 7 Supplemental Questions

There were no supplemental questions identified for this review.

# 8 Comparison with Other Literature

The CADTH Clinical Guidance Panel and the CADTH Methods Team did not identify other relevant literature providing supporting information for this review.

# 9 About this Document

This Clinical Guidance Report was prepared by the CADTH Lymphoma Clinical Guidance Panel and supported by the CADTH Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on brentuximab vedotin (Adcetris) for HL. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant CADTH Economic Guidance Report. Details of the pCODR review process can be found on the CADTH website (www.cadth.ca/pcodr).

CADTH considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the Procedures for the CADTH pan-Canadian Oncology Drug Review. The sponsor, as the primary data owner, did not agree to the disclosure of some clinical information which was provided to pERC for their deliberations, and this information has been redacted in this publicly posted Guidance Report.

# Appendix 1: Literature Search Strategy and Detailed Methodology

## 1. Literature search via Ovid platform

**Database(s):** Cochrane Central Register of Controlled Trials (CENTRAL); Embase (1974 to present); MEDLINE All (1946 to present)

| # | Searches | Results |
|---|---|---|
| 1 | ("brentuximab/AVD" or "AVD/brentuximab" or A+AVD or BV+AVD or (BV adj3 AVD)).ti,ab,ot,kf,kw,hw,nm,rn. | 276 |
| 2 | Brentuximab Vedotin/ or 7XL5ISS668.rn,nm. or (Adcetris* or brentuximab* or adtsetrys* or cac10-vcmmae or cac10vcmmae or cac10-1006 or cac101006 or sgn-35 or sgn35).ti,ab,ot,kf,kw,hw,nm,rn. | 5099 |
| 3 | doxorubicin/ or 80168379AG.rn,nm. or (doxorubicin* or adiamycin* or adriablastin* or adriblastin* or adriacin* or adriamicin* or adriamycin* or adrim* or adrimedac* or adrubicin* or amminac* or caelix* or caelyx* or "caelyx/doxil" or carcinocin* or doxil* or doxo-cell or doxolem* or doxor lyo or doxorubin* or doxotec* or evacet* or farmiblastin* or ifadox* or lipodox* or myocet* or onkodox* or rastocin* or resmycin* or ribodoxo* or rubex* or rubidox* or sarcodoxome* or DXR or einecs 245-495-6 or fi-106 or fi106 or hsdb 3070 or nci-c01514 or ndc 38242-874 or nsc-123127 or nsc123127 or mcc-465 or mcc465 or rp-25253 or rp25253 or "tlc d 99" or ccris 739).ti,ab,ot,kf,kw,hw,nm,rn. | 279668 |
| 4 | Vinblastine/ or (5V9KLZ54CY or N00W22YO2B).rn,nm. or (vinblastin* or velban* or alkaban* or blastovin* or cellblastin* or cytoblastin* or exal or lemblastine* or leukoblastin* or nincaluicolflastin* or rozevin* or uniblastin* or vin blastin* or vincaleukoblastin* or vincolaukoblastin* or vincaleucoblastin* or vincolaucoblastin* or vinleucoblastin* or velba* or velbe* or velsar* or vincoblastin* or vinblastinsulfat-gry or xintoprost* or vlb or vr-8 or nsc 47842 or le 29060 or le29060 or 29060 le or nsc 49842 or nsc49842 or ai3-52943 or einecs 205-606-0 or ccris 2584).ti,ab,ot,kf,kw,hw,nm,rn. | 55811 |
| 5 | dacarbazine/ or 7GR28W0FJI.rn,nm. or (dacarbazin* or imidazole carboxamide* or imidazole carboxamine* or di-me-triazenoimidazolecarboxamide* or di-me-triazenoimidazolecarboxamine* or dimethyltriazenoimidazole carboxamide* or dimethyltriazenoimidazole carboxamine* or dimethyltriazenoimidazolecarboxamide* or dimethyltriazenoimidazolecarboxamine* or biocarbazin* or dacatic* or deticene* or detimedac* or decarbazine* or DIC or ICDT or nsc 45388 or nsc45388 or nsc 45 388 or dtic or "d.t.i.c" or dticdome or icdmt or ai3-52825 or einecs 224-396-1 or hsdb 3219 or icdmt or nci-c04717 or ccris 190).ti,ab,ot,kf,kw,hw,nm,rn. | 52139 |
| 6 | 2 and 3 and 4 and 5 | 564 |
| 7 | AVD.ti,ab,ot,kf,kw,hw,nm,rn. | 2209 |
| 8 | 2 and 7 | 194 |
| 9 | (brentuximab vedotin/ or brentuximab.ti.) and chemotherapy.ti. | 202 |
| 10 | 1 or 6 or 8 or 9 | 861 |

| | | |
|---|---|---|
| 11 | 10 use cctr | 182 |
| 12 | 10 use medall | 79 |
| 13 | ("brentuximab/AVD" or "AVD/brentuximab" or A+AVD or BV+AVD or (BV adj3 AVD)).ti,ab,kw,dq. | 275 |
| 14 | *brentuximab vedotin/ or (Adcetris* or brentuximab* or adtsetrys* or cac10-vcmmae or cac10vcmmae or cac10-1006 or cac101006 or sgn-35 or sgn35).ti,ab,kw,dq. | 3634 |
| 15 | *doxorubicin/ or (doxorubicin* or adiamycin* or adriablastin* or adriblastin* or adriacin* or adriamicin* or adriamycin* or adrim* or adrimedac* or adrubicin* or amminac* or caelix* or caelyx* or "caelyx/doxil" or carcinocin* or doxil* or doxo-cell or doxolem* or doxor lyo or doxorubin* or doxotec* or evacet* or farmiblastin* or ifadox* or lipodox* or myocet* or onkodox* or rastocin* or resmycin* or ribodoxo* or rubex* or rubidox* or sarcodoxome* or DXR or einecs 245-495-6 or fi-106 or fi106 or hsdb 3070 or nci-c01514 or ndc 38242-874 or nsc-123127 or nsc123127 or mcc-465 or mcc465 or rp-25253 or rp25253 or "tlc d 99" or ccris 739).ti,ab,kw,dq. | 169496 |
| 16 | *vinblastine/ or (vinblastin* or velban* or alkaban* or blastovin* or cellblastin* or cytoblastin* or exal or lemblastine* or leukoblastin* or nincaluicolflastin* or rozevin* or uniblastin* or vin blastin* or vincaleukoblastin* or vincolaukoblastin* or vincaleucoblastin* or vincolaucoblastin* or vinleucoblastin* or velba* or velbe* or velsar* or vincoblastin* or vinblastinsulfat-gry or xintoprost* or vlb or vr-8 or nsc 47842 or le 29060 or le29060 or 29060 le or nsc 49842 or nsc49842 or ai3-52943 or einecs 205-606-0 or ccris 2584).ti,ab,kw,dq. | 31316 |
| 17 | *dacarbazine/ or (dacarbazin* or imidazole carboxamide* or imidazole carboxamine* or di-me-triazenoimidazolecarboxamide* or di-me-triazenoimidazolecarboxamine* or dimethyltriazenoimidazole carboxamide* or dimethyltriazenoimidazole carboxamine* or dimethyltriazenoimidazolecarboxamide* or dimethyltriazenoimidazolecarboxamine* or biocarbazin* or dacatic* or deticene* or detimedac* or decarbazine* or DIC or ICDT or nsc 45388 or nsc45388 or nsc 45 388 or dtic or "d.t.i.c" or dticdome or icdmt or ai3-52825 or einecs 224-396-1 or hsdb 3219 or icdmt or nci-c04717 or ccris 190).ti,ab,kw,dq. | 36176 |
| 18 | 14 and 15 and 16 and 17 | 202 |
| 19 | AVD.ti,ab,kw,dq. | 2163 |
| 20 | 14 and 19 | 192 |
| 21 | (*brentuximab vedotin/ or brentuximab.ti.) and chemotherapy.ti. | 148 |
| 22 | 13 or 18 or 20 or 21 | 464 |
| 23 | 22 use oemezd | 223 |
| 24 | (conference review or conference abstract).pt. | 3776673 |
| 25 | 23 not 24 | 85 |
| 26 | 12 or 25 | 164 |

| | | |
|---|---|---|
| 27 | limit 26 to english language | 156 |
| 28 | 11 or 27 | 338 |
| 29 | remove duplicates from 28 | 266 |
| 30 | 23 and 24 | 138 |
| 31 | limit 30 to english language | 138 |
| 32 | limit 31 to yr="2015 -Current" | 111 |
| 33 | 29 or 32 | 377 |

**2. Literature search via PubMed**

A limited PubMed search was performed to retrieve citations not found in the MEDLINE search.

| Search | Query | Items Found |
|---|---|---|
| #12 | Search #10 AND #11 | 2 |
| #11 | Search publisher[sb] | 393571 |
| #10 | Search #1 OR #6 OR #8 OR #9 | 81 |
| #9 | Search (brentuximab vedotin[mh] OR brentuximab[ti]) AND chemotherapy[ti] | 26 |
| #8 | Search #2 AND #7 | 25 |
| #7 | Search AVD[tiab] | 660 |
| #6 | Search #2 AND #3 AND #4 AND #5 | 51 |
| #5 | Search Dacarbazine[mh] OR 7GR28W0FJI[rn] OR dacarbazin*[tiab] OR imidazole carboxamide*[tiab] OR imidazole carboxamine*[tiab] OR di-me-triazenoimidazolecarboxamide*[tiab] OR di-me-triazenoimidazolecarboxamine*[tiab] OR dimethyltriazenoimidazole carboxamide*[tiab] OR dimethyltriazenoimidazole carboxamine*[tiab] OR dimethyltriazenoimidazolecarboxamide*[tiab] OR dimethyltriazenoimidazolecarboxamine*[tiab] OR biocarbazin*[tiab] OR dacatic*[tiab] OR deticene*[tiab] OR detimedac*[tiab] OR decarbazine*[tiab] OR DIC[tiab] OR ICDT[tiab] OR nsc 45388[tiab] OR nsc45388[tiab] OR nsc 45 388 OR dtic[tiab] OR "d.t.i.c"[tiab] OR dticdome[tiab] OR icdmt[tiab] OR ai3-52825[tiab] OR einecs 224-396-1[tiab] OR hsdb 3219[tiab] OR icdmt[tiab] OR nci-c04717[tiab] OR ccris 190[tiab] | 17494 |
| #4 | Search Vinblastine[mh] OR 5V9KLZ54CY[rn] OR N00W22YO2B[rn] OR vinblastin*[tiab] OR velban*[tiab] OR alkaban*[tiab] OR blastovin*[tiab] OR cellblastin*[tiab] OR cytoblastin*[tiab] OR exal[tiab] OR lemblastine*[tiab] OR leukoblastin*[tiab] OR nincaluicolflastin*[tiab] OR rozevin*[tiab] OR uniblastin*[tiab] | 16515 |

| Search | Query | Items Found |
|---|---|---|
| | OR vin blastin*[tiab] OR vincaleukoblastin*[tiab] OR vincolaukoblastin*[tiab] OR vincaleucoblastin*[tiab] OR vincolaucoblastin*[tiab] OR vinleucoblastin*[tiab] OR velba*[tiab] OR velbe*[tiab] OR velsar*[tiab] OR vincoblastin*[tiab] OR vinblastinsulfat-gry[tiab] OR xintoprost*[tiab] OR vlb[tiab] OR vr-8[tiab] OR nsc 47842[tiab] OR le 29060[tiab] OR le29060[tiab] OR 29060 le[tiab] OR nsc 49842[tiab] OR nsc49842[tiab] OR ai3-52943[tiab] OR einecs 205-606-0[tiab] OR ccris 2584[tiab | |
| #3 | Search Doxorubicin[mh] OR 80168379AG[rn] OR doxorubicin*[tiab] OR adiamycin*[tiab] OR adriablastin*[tiab] OR adriblastin*[tiab] OR adriacin*[tiab] OR adriamicin*[tiab] OR adriamycin*[tiab] OR adrim*[tiab] OR adrimedac*[tiab] OR adrubicin*[tiab] OR amminac*[tiab] OR caelix*[tiab] OR caelyx*[tiab] OR "caelyx/doxil"[tiab] OR carcinocin*[tiab] OR doxil*[tiab] OR doxo-cell[tiab] OR doxolem*[tiab] OR doxor lyo[tiab] OR doxorubin*[tiab] OR doxotec*[tiab] OR evacet*[tiab] OR farmiblastin*[tiab] OR ifadox*[tiab] OR lipodox*[tiab] OR myocet*[tiab] OR onkodox*[tiab] OR rastocin*[tiab] OR resmycin*[tiab] OR ribodoxo*[tiab] OR rubex*[tiab] OR rubidox*[tiab] OR sarcodoxome*[tiab] OR DXR[tiab] OR einecs 245-495-6[tiab] OR fi-106[tiab] OR fi106[tiab] OR hsdb 3070[tiab] OR nci-c01514[tiab] OR ndc 38242-874[tiab] OR nsc-123127[tiab] OR nsc123127[tiab] OR mcc-465[tiab] OR mcc465[tiab] OR rp-25253[tiab] OR rp25253[tiab] OR "tlc d 99"[tiab] OR ccris 739[tiab] | 77526 |
| #2 | Search Brentuximab Vedotin[mh] OR 7XL5ISS668[rn] OR Adcetris*[tiab] OR brentuximab*[tiab] OR adtsetrys*[tiab] OR cac10-vcmmae[tiab] OR cac10vcmmae[tiab] OR cac10-1006[tiab] OR cac101006[tiab] OR sgn-35[tiab] OR sgn35[tiab] | 1008 |
| #1 | Search "brentuximab/AVD"[tiab] OR "AVD/brentuximab"[tiab] OR A+AVD[tiab] OR BV+AVD[tiab] OR (BV[tiab] AND AVD[tiab]) | 23 |

3. **Cochrane Central Register of Controlled Trials (CENTRAL)**
   (searched via Ovid)

4. **Grey literature search via:**

   Clinical trial registries:

   US National Library of Medicine. ClinicalTrials.gov
   https://clinicaltrials.gov/

   World Health Organization

   http://apps.who.int/trialsearch/

   Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials

   http://www.canadiancancertrials.ca/

   Search: Adcetris/brentuximab vedotin, doxorubicin, vinblastine, dacarbazine, Hodgkin's lymphoma

Select international agencies including:

US Food and Drug Administration (FDA)

https://www.fda.gov/

European Medicines Agency (EMA)

https://www.ema.europa.eu/

Search: Adcetris/brentuximab vedotin, doxorubicin, vinblastine, dacarbazine, Hodgkin's lymphoma

Conference abstracts:

American Society of Clinical Oncology (ASCO)

https://www.asco.org/

European Society for Medical Oncology (ESMO)

https://www.esmo.org/

American Society of Hematology (ASH)

http://www.hematology.org/

Search: Adcetris/brentuximab vedotin, doxorubicin, vinblastine, dacarbazine, Hodgkin's lymphoma — last five years

**Detailed Methodology**

The literature search for clinical studies was performed by an information specialist from the pCODR Methods Team using the abovementioned search strategy, which was peer-reviewed according to the *PRESS Peer Review of Electronic Search Strategies* checklist (https://www.cadth.ca/resources/finding-evidence/press).[53]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946– ) via Ovid, Embase (1974– ) via Ovid, the Cochrane Central Register of Controlled Trials (CENTRAL) via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Adcetris (brentuximab vedotin) in combination with doxorubicin, vinblastine, and dacarbazine.

No filters were applied to limit the retrieval by study type. The search was also limited to English-language documents but not limited by publication year.

The search is considered up to date as of August 20, 2020.

Grey literature (literature that is not commercially published) was identified by searching websites from relevant sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist (https://www.cadth.ca/grey-matters).[54] Included in this search were the websites of regulatory agencies (US Food and Drug Administration and European Medicines Agency), clinical trial registries (US National Institutes of Health's clinicaltrials.gov, World Health Organization's International Clinical Trials Registry, and Canadian Partnership Against Cancer Corporation's Canadian Cancer Trials), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO), and American Society of Hematology (ASH) were

searched manually for conference years not available in Embase. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the CADTH Clinical Guidance Panel. As well, the manufacturer of the drug was contacted for additional information, as required by the pCODR Review Team.

**Study Selection**

One member of the CADTH Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. One member of the pCODR Methods Team made the final selection of studies to be included in the review.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

**Quality Assessment**

Assessment of study bias was performed by one member of the CADTH Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

**Data Analysis**

No additional data analyses were conducted as part of the pCODR review.

**Writing of the Review Report**

This report was written by the Methods Team, the Clinical Guidance Panel and CADTH:

- The Methods Team wrote a summary of background clinical information, a systematic review of the evidence, interpretation of the systematic review, and summaries of evidence for supplemental questions.
- The CADTH Clinical Guidance Panel provided guidance and developed conclusions on the net clinical benefit of the drug.
- CADTH wrote summaries of the input provided by patient advocacy groups, by the Provincial Advisory Group (PAG), and by Registered Clinicians.

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