pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

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

pERC Final Recommendation
This pCODR Expert Review Committee (pERC) Final Recommendation is based on a reconsideration of the Initial Recommendation and feedback from eligible stakeholders. This pERC Final Recommendation supersedes the pERC Initial Recommendation.

Drug: Brentuximab Vedotin (Adcetris) **Submitted Reimbursements Request:** For the treatment of previously untreated adult patients with systemic anaplastic large-cell lymphoma, peripheral T-cell lymphoma not otherwise specified or angioimmunoblastic T-cell lymphoma, whose tumours express CD30 plus cyclophosphamide, doxorubicin, and prednisone.	
Submitted By: Seattle Genetics, Inc.	**Manufactured By:** Seattle Genetics, Inc.
NOC Date: November 22, 2019	**Submission Date:** October 8, 2019
Initial Recommendation: April 2, 2020	**Final Recommendation:** June 4, 2020

Approximate Per-Patient Drug Costs, per Month (28 Days)	At the recommended dose of 1.8 mg/kg every three weeks, brentuximab costs $14,520.00 per 21-day cycle.

pERC RECOMMENDATION

☒ **Reimburse**

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

☐ **Do not reimburse**

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

pERC recommends reimbursement of brentuximab vedotin (BV) for the treatment of previously untreated adult patients with systemic anaplastic large-cell lymphoma (sALCL), peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), or angioimmunoblastic T-cell lymphoma (AITL), whose tumours express CD30, plus cyclophosphamide, doxorubicin, and prednisone (CHP).

Patients with anaplastic lymphoma kinase (ALK) positive sALCL should have an International Prognostic Index (IPI) score of ≥ 2. Treatment should be continued for six or eight cycles, until disease progression or unacceptable toxicity, whichever comes first.

pERC made this recommendation because it was satisfied that, compared with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), there is a net clinical benefit of BV plus CHP for previously untreated adult patients with sALCL based on statistically significant and clinically meaningful improvements in progression-free survival (PFS) and overall survival (OS), a manageable toxicity profile, no detriment in quality of life (QoL), and a need for treatment options that lead to long-term remission and potential cure.

pERC considered that, compared with CHOP, there may be a net clinical benefit of BV plus CHP for previously untreated adult patients with PTCL-NOS and AITL subtypes based on the fact that these patients were included in the intention-to-treat analysis with OS results that were consistent with the overall study results, similar adverse event profiles between CHP plus BV and CHOP, no apparent detriment in QoL, and a need for treatment options that lead to long-term remission and potential cure in this small patient population.

pERC concluded that BV plus CHP aligns with patient values in that it leads to prolonged survival and remission, has a manageable toxicity profile with no detrimental effect on QoL, and offers an additional treatment choice.

pERC concluded that, at the submitted price, BV plus CHP may be cost-effective compared with CHOP in patients with sALCL, PTCL-NOS, and AITL whose tumours express CD30. pERC noted that there was uncertainty related to the long-term extrapolation of OS benefit of BV in combination with CHP. pERC also concluded that the submitted budget impact is likely underestimated and the actual budget impact may be substantially greater.

POTENTIAL NEXT STEPS FOR STAKEHOLDERS

Price Arrangement to Improve Cost-Effectiveness and Affordability of BV in Combination With CHP
Given that pERC concluded that there is a net clinical benefit of BV plus CHP compared with CHOP in patients with sALCL and that there may be a net clinical benefit in patients with PTCL-NOS and AITL in this setting, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness and affordability of BV plus CHP to an acceptable level.

Optimal Sequencing of Available Therapies After Progression on BV in Combination With CHP
pERC concluded that the optimal sequencing of therapies for patients with sALCL, PTCL-NOS, and AITL whose tumours express CD30 is unknown. Therefore, pERC was unable to make an evidence-informed recommendation on sequencing of treatments. pERC recognized that provinces will need to address this issue upon implementation of a reimbursement recommendation for BV plus CHP and noted that collaboration among provinces to develop a national, uniform approach to optimal sequencing would be of great value.

Time-Limited Need for Patients Who Are Currently Receiving Frontline Chemotherapy Treatment and Who Have not Progressed
At the time of implementing a reimbursement recommendation for BV plus CHP, jurisdictions may want to consider addressing the time-limited need to offer BV plus CHP to patients who are currently receiving frontline chemotherapy treatment and who have not progressed.

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

SUMMARY OF pERC DELIBERATIONS

Peripheral T-cell lymphoma (PTCL) is a broad category of T-cell lymphoma with several heterogeneous subtypes including systemic anaplastic large-cell lymphoma (sALCL), PTCL- not otherwise specified (PTCL-NOS), and angioimmunoblastic T-cell lymphoma (AITL). These subtypes account for almost 70% of all cases of PTCL, and it is estimated that there are around 560 new cases per year in Canada. Current Canadian standard of care of patients with PTCL is either CHOP or cyclophosphamide, doxorubicin, vincristine, etoposide and prednisone (CHEOP) with or without autologous stem cell transplantation consolidation (SCT). Upon relapse, a variety of therapeutic approaches are available. For patients who are candidates for SCT but have not received SCT previously, multi-drug salvage chemotherapy is widely used, followed by SCT if indicated. For patients who are not candidates for aggressive therapy, or have relapsed post-SCT, single drug palliative therapies include BV (for patients who express CD30), histone deacetylase inhibitors (e.g., Romidepsin, Belinostat), and Pralatrexate. In general, treatment outcomes have been poor with conventional chemotherapy regimens. In a Canadian series, five-year OS for PTCL-NOS, AITL, anaplastic lymphoma kinase (ALK)-positive sALCL and ALK-negative sALCL was 35%, 36%, 58%, and 34% (Savage et al., 2004).Therefore, pERC agreed with the CADTH pan-Canadian Oncology Drug Review (pCODR) Clinical Guidance Panel (CGP) that there is a need for effective treatment options that lead to long-term remission and survival and potential cure in this setting.

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

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

pERC deliberated upon one international, multi-centred, double-blind, double-dummy, active-controlled phase III trial (ECHELON-2) that evaluated the efficacy and safety of BV plus CHP versus CHOP for the treatment of CD30-positive PTCL. pERC noted that the requested reimbursement population was specifically for patients with sALCL, PTCL-NOS, and AITL histological subtypes whereas the trial population included the following subtypes: sALCL (ALK-positive sALCL with an International Prognostic Index (IPI) score of equal to or greater than two, ALK-negative sALCL), PTCL-NOS, AITL, adult T-cell leukemia or lymphoma (ATLL), and enteropathy-associated T-cell lymphoma (EATL). The Committee noted that the majority of patients in the trial belonged to the sALCL subgroup.

pERC considered that progression-free survival (PFS), the primary outcome of the trial, was statistically significant and clinically meaningful in favour of BV plus CHP. Key secondary outcomes, such as PFS in the subset of patients with sALCL and overall survival (OS), were also statistically significant in favour of BV plus CHP. pERC noted that, except for the subgroup analysis of PFS by sALCL, subgroup analyses were considered exploratory because the ECHELON-2 trial was not designed to test specific hypotheses for subgroups. pERC agreed that there may be a net clinical benefit to the combination of BV plus CHP compared with CHOP in the treatment of patients with PTCL-NOS and AITL as the subgroup results for OS were consistent with the overall study results, both (PTCL-NOS and AITL) are nodal PTCL similar to sALCL, and CD30-expression is the target for the mechanism of action of BV. pERC also discussed that due to the rarity of these subtypes with CD30-expressing tumours, RCTs will likely not be feasible. However, pERC acknowledged that, given the trial was not powered to detect treatment effects within subgroups, there was considerable uncertainty around the magnitude of the OS benefit. Additionally, pERC considered the generalizability of the ECHELON-2 trial results to the subtypes of ATLL and EATL. While pERC acknowledged the small sample size, pERC agreed that it may be reasonable to generalize the ECHELON-2 trial results to patients with ATLL and EATL, as these patients were included in the intention-to-treat (ITT) analyses, it is unlikely that there will be trials specifically designed for this small group of patients, and there is no apparent biological rationale to assume that outcomes of BV plus CHP therapy would be different between subtypes of CD30-positive PTCL. pERC recognized that eligibility for BV plus CHP for patients with ATLL and EATL subtypes could be addressed on a case-by-case basis. Furthermore, pERC considered that according to the inclusion criteria of the ECHELON-2 trial, enrolment of patients with ALK-positive sALCL was limited to those with an IPI score of equal to or greater than two. pERC agreed with the CGP that there are no data to support the generalizability of treatment benefit to patients with ALK-positive sALCL with an IPI score of less than two.

pERC also discussed the safety profile and concluded that BV plus CHP has a manageable toxicity profile.

pERC noted that in the ECHELON-2 trial, BV plus CHP was well-tolerated and had a similar safety profile to that of CHOP. Overall, the incidence of treatment-emergent adverse events (TEAEs) reported between the two groups was comparable. Additionally, pERC discussed the available patient-reported outcomes data from the ECHELON-2 trial and noted that overall quality of life (QoL) was similar between the two study groups and BV plus CHP did not appear to have a detrimental effect on QoL compared with CHOP. pERC acknowledged that this analysis was exploratory and should be interpreted with caution.

Overall, pERC was satisfied that, compared with CHOP, there is a net clinical benefit of BV plus CHP in previously untreated adult patients with sALCL, based on statistically significant and clinically meaningful improvements in PFS and OS, a manageable toxicity profile, no detriment in QoL, and a need for treatment options that lead to long-term remission and potential cure. pERC considered that, compared with CHOP, there may be a net clinical benefit of BV plus CHP for previously untreated adult patients with PTCL-NOS and AITL subtypes based on the fact that these patients were included in the ITT analyses with OS results that were consistent with the overall study results, similar adverse event (AE) profiles between CHP plus BV and CHOP, no apparent detriment in QoL, and a need for treatment options that lead to long-term remission and potential cure in this small patient population.

pERC deliberated on input from one patient advocacy group concerning BV plus CHP. pERC noted that a very small number of patients had experience with BV plus CHP as frontline treatment for PTCL. The Committee noted that overall, BV plus CHP was well-tolerated and that respondents reported that the most difficult side effect to tolerate was fatigue, which worsened throughout treatment. pERC discussed that patients value having another treatment option, increased survival, longer remission, improved QoL, and fewer side effects. pERC noted that the majority of patient respondents reported that they are willing to tolerate significant side effects from new drug therapies. Overall, pERC concluded that BV plus CHP aligns with patient values in that it leads to prolonged survival and remission, has a manageable toxicity profile with no detrimental effect on QoL, and offers an additional treatment choice.

pERC deliberated on the cost-effectiveness of BV plus CHP compared with CHOP and CHOP plus etoposide (CHOEP). pERC discussed the limitations of the economic model described by the CADTH Economic Guidance Panel (EGP) and noted that due to the uncertainty regarding long-term extrapolation of OS, there was uncertainty in the magnitude of clinical benefit associated with BV plus CHP.

Upon reconsideration of the pERC Initial Recommendation, the Committee had an extensive discussion on the feedback provided by PAG suggesting that the Initial Recommendation would lend itself better to a positive recommendation conditional on cost-effectiveness being improved to an acceptable level. PAG noted that there was considerable uncertainty in the clinical benefit of BV plus CHP for previously untreated adult patients with PTCL-NOS and AITL subtypes and cost-effectiveness estimates across all eligible patients. In response to PAG's feedback, pERC reiterated that while the trial was not designed to detect treatment effects within subgroups, the PTCL-NOS and AITL subgroups were included in the ITT analysis and had shown OS results that were consistent with the overall study results. pERC reiterated that there may be a net clinical benefit to the combination of BV plus CHP compared with CHOP in the treatment of patients with PTCL-NOS and AITL. Further, the Committee discussed that the uncertainty around the CADTH reanalyzed incremental cost-effectiveness ratio (ICER) estimates had been appropriately explored by the EGP (i.e., conservative extrapolation, waning of treatment effect). pERC noted that it was not possible to determine the impact of specific histological subgroups on the CADTH ICER estimate. pERC recognized that jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness and affordability of BV plus CHP to a level acceptable to the provinces.

pERC also noted that the effect associated with subsequent treatment had not been explicitly modelled as the sponsor assumed it was implicitly incorporated when applying the PFS and OS outcomes from the trial, which was not considered to be appropriate by pERC. However, pERC also noted that even though subsequent treatment effects were not included in the model, costs associated with subsequent treatments were appropriately included. pERC concluded that, at the submitted price, BV plus CHP may be cost-effective compared with CHOP in patients with sALCL, PTCL-NOS, and AITL whose tumours express CD30. pERC noted that there was uncertainty related to the long-term extrapolation of OS benefit of BV in combination with CHP.

pERC also discussed the budget impact and noted that the factor that most influence the budget impact is the market shares of BV plus CHP. pERC noted that the EGP considered the market share of year one to

year three to be underestimated and that an alternative market share was used by the EGP, which yielded a higher budget impact over a three-year period compared with the sponsor's estimate.

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

EVIDENCE IN BRIEF

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

- a pCODR systematic review
- other literature in the Clinical Guidance Report that provided clinical context
- an evaluation of the manufacturer's economic model and budget impact analysis
- guidance from the pCODR clinical and economic review panels
- input from one patient advocacy group: Lymphoma Canada (LC)
- input from registered clinicians: One joint input on behalf of five clinicians from British Columbia Cancer and one individual input by a single hematologist from Cancer Care Ontario Hematology drug advisory committee (DAC)
- input from pCODR's Provincial Advisory Group (PAG).

Feedback on the pERC Initial Recommendation was also provided by:

- one patient advocacy group: LC
- one individual registered clinician from Cancer Care Ontario Hematology DAC
- the PAG
- the sponsor, Seattle Genetics Inc.

The pERC Initial Recommendation was to recommend the reimbursement of brentuximab vedotin (BV) for the treatment of previously untreated adult patients with systemic anaplastic large-cell lymphoma (sALCL), peripheral T-cell lymphoma not otherwise specified (PTCL-NOS) or angioimmunoblastic T-cell lymphoma (AITL), whose tumours express CD30, plus cyclophosphamide, doxorubicin, and prednisone (CHP).

Feedback on the pERC Initial Recommendation indicated that the patient advocacy group, the individual registered clinician, and the sponsor agreed with the Initial Recommendation and supported conversion to the Final Recommendation. The PAG partially agreed with the Initial Recommendation and did not support conversion to the Final Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of this review is to evaluate the efficacy and safety of BV plus CHP compared to combination chemotherapy with CHOP or CHOP-like regimens for the treatment of previously untreated adult patients with sALCL, PTCL-NOS, or AITL, whose tumours express CD30.

Studies included: One randomized, placebo-controlled, phase III trial

The pCODR systematic review included one international, multi-centred, double-blind, double-dummy, active-controlled phase III trial: ECHELON-2. The ECHELON-2 trial evaluated the efficacy and safety of BV plus CHP versus CHOP for the treatment of CD30-positive PTCL.

A total of 452 patients were randomized (1:1) in ECHELON-2, with 226 patients assigned to BV plus CHP and 226 patients assigned to CHOP. After randomization, all patients were treated with the CHP components of the CHOP regimen, which included cyclophosphamide 750 mg/m^2 and doxorubicin 50 mg/m^2 intravenously on day 1 of each cycle and prednisone 100 mg orally once daily on days one to five of each cycle. The number of cycles (six or eight) was decided at the investigator's discretion at registration. A double-dummy placebo design was used, such that the experimental group received BV and a placebo form of vincristine and patients in the CHOP group received vincristine and a placebo form of BV. Patients in the BV plus CHP group received 1.8 mg/kg of BV intravenously on day 1 of each cycle and patients in the CHOP group received vincristine 1.4 mg/m^2 (maximum 2.0 mg) intravenously on day 1 of each cycle after administration of CHP.

Crossover was not permitted at any time during the study. If a patient relapsed during or after treatment, unblinding could be requested and off-study therapy could be subsequently administered. All patients received treatment until the completion of 6 to 8 cycles, the date of first documentation of progressive disease (PD), death due to any cause, or receipt of subsequent anticancer chemotherapy to treat residual or PD, whichever occurred first.

The median number of treatment cycles per patient was six (minimum one; maximum eight) for BV plus CHP and six (minimum one; maximum eight) for the CHOP group. The median duration of treatment was 18.1 weeks (minimum three; maximum 34) and 18 weeks (minimum three; maximum 31) in the BV plus CHP and CHOP groups, respectively.

As of the August 15, 2018 data cut-off date for the primary efficacy analysis, 296 of the 452 randomized patients (65%) remained in long-term follow-up; 157 (69%) patients in the BV plus CHP group, and 139 (62%) in the CHOP group. A total of 370 (82%) patients have completed treatment; 192 (85%) patients in the BV plus CHP group and 178 (79%) in the CHOP group.

Patient populations: Median age 58 years; majority of patients with sALCL (70%) and minority received consolidative treatments (23%)

Overall, the baseline characteristics were well-balanced between the two treatment groups. The median age was 58 years, with 69.2% of patients falling in the 19 to 64 age range. The majority of patients were male (62.8%), and most patients were white (62.2%) or of Asian descent (21.9%). Seventy percent of the patient population was diagnosed with sALCL, with almost half of all patients diagnosed with ALK-negative sALCL (48.2%). Most patients had an Eastern Cooperative Oncology Group Performance Status of 0 (39.2%) or 1 (38.9%), with 21.7% having a performance status of 2. A little more than half of all randomized patients had stage IV disease at diagnosis (53.1%) and 78.8% had IPI scores ≥ 2.

Consolidative therapies, including SCT (with the intent pre-specified before the first cycle of chemotherapy) and/or radiotherapy after treatment were permitted at the investigator's discretion after at least six cycles of treatment. A total of 27% of patients randomized to the BV plus CHP group and 19.5% of patients in the CHOP group received consolidative treatments (i.e., consolidative SCT or consolidative radiotherapy).

A total of 65 patients (29%) in the BV plus CHP group and 96 patients (42%) in the CHOP group received subsequent anticancer therapy. Patients may have received more than one type of therapy. Of those patients that received subsequent therapy, 59 patients (26%) in the BV plus with CHP group and 94 patients (42%) in the CHOP group received systemic therapy for residual or PD, and among those patients 23 (10%) in the BV plus CHP group and 49 (22%) in the CHOP group received BV-containing regimens.

Key efficacy results: Statistically significant difference in PFS and OS in favour of BV plus CHP; consistent results seen in pre-specified, type I error-controlled analysis of PFS for the sALCL subgroup

The primary outcome of the trial was PFS per blinded institutional review facility (IRF), which was defined as the time from the date of randomization to the date of first documentation of PD, death due to any cause, or receipt of subsequent anticancer chemotherapy to treat residual or PD, whichever occurred first. Receipt of post-treatment consolidative radiotherapy, post-treatment chemotherapy for the purpose of mobilizing peripheral stem cells, or consolidative autologous or allogeneic SCT was not considered disease progression or as having started new anticancer therapy. Key secondary outcomes included PFS per IRF in the subset of patients with sALCL, complete remission rate per IRF following completion of study treatment, OS, objective response rate (ORR) per IRF following completion of study treatment, safety, and QoL.

Treatment with BV plus CHP resulted in a statistically significant improvement in PFS per blinded IRF in the ITT population compared to CHOP. PFS per IRF was significantly improved in the BV plus CHP group compared with the CHOP group (stratified HR = 0.71; 95% CI, 0.54 to 0.93; P = 0.011). The median PFS for the BV plus CHP and CHOP groups was 48.2 months and 20.8 months, respectively.

Treatment with BV plus CHP was also superior to treatment with CHOP for other key secondary outcomes. The complete remission rate was significantly higher in the BV plus CHP group versus CHOP (68% versus 56%, respectively), there were significantly fewer deaths in the BV plus CHP group versus the CHOP group (stratified HR = 0.66; 95% CI, 0.46 to 0.95; P = 0.0244), and the ORR at the end of treatment was significantly higher with BV plus CHP versus CHOP.

The results of the pre-specified and type I error-controlled analysis of PFS per IRF for the sALCL subgroup of patients were consistent with the results of the primary outcome of PFS. PFS per IRF for patients with sALCL was significantly improved in the BV plus CHP group compared with the CHOP group (stratified HR = 0.59; 95% CI, 0.42 to 0.84; P = 0.0031). The median PFS per IRF for patients with sALCL was 55.66 months

(95% CI, 48.20 to not reached) on the BV plus CHP group versus 54.18 months (95% CI, 13.44 to not reached) on the CHOP group.

Subgroup analyses were considered exploratory because the ECHELON-2 trial was not designed to test specific hypotheses for subgroups. The only subgroup for which an alpha-controlled hypothesis test was pre-specified is the subgroup of sALCL patients for PFS. The exploratory analysis for the AITL subgroup showed a PFS HR of 1.40 (95% CI, 0.64 to 3.07), and an OS HR of 0.87 (95% CI, 0.29 to 2.58) for BV plus CHP compared to CHOP. The exploratory analysis for the PTCL-NOS subgroup showed a PFS HR of 0.75 (95% CI, 0.41 to 1.37), and an OS HR of 0.83 (95% CI, 0.38 to 1.80) for BV plus CHP compared to CHOP.

Patient-reported outcomes: Overall no difference between treatment arms

QoL outcomes (an exploratory end point of the ECHELON-2 trial), were collected using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30), the Functional Assessment of Cancer Treatment Gynecologic Oncology Group - Neurotoxicity (FACT/GOG-NTX) instrument, and the European Quality of Life 5-Dimensions Questionnaire (EQ-5D-3L).

The descriptive health-related QoL analyses were conducted in the ITT population. Statistical modelling was performed as post-hoc analyses. The overall response rate for the patient-reported outcomes questionnaires was high (> 90%) in both treatment groups until end-of-treatment visit and remained mostly > 80% for the EORTC QLQ-C30 and the EQ-5D instruments and > 70% for the FACT/GOG-NTX instrument during follow-up time until month 24.

The mean EORTC symptom, functional, and global health scores were lower at baseline in the BV plus CHP group compared with the CHOP group. However, during the treatment period the scores improved in both treatment groups and returned to near-normal values during long-term follow-up. Using linear mixed models to analyze the change from baseline scores, some statistically significant differences between the two groups in favour of CHOP were detected; however, none of the differences in scores, aside from diarrhea at cycle 7 in favour of CHOP, were clinically meaningful based on the published minimal important difference (MID) of 10.

For the FACT/GOG-NTX neurotoxicity subscale, the sponsor noted that scores were not meaningfully different between the treatment groups up to cycle 8. At the end-of-treatment visit, the score was lower for the BV plus CHP group compared with the CHOP group, which is in line with the higher rate of unresolved neuropathy in the BV plus CHP group. However, the neurotoxicity scores returned to baseline values during long-term follow-up. Results were analyzed using linear mixed models and did not demonstrate any differences between the treatment groups in the change from baseline scores across the treatment cycles.

Data from both the EQ-5D and the EuroQol Visual Analogue Scale (EQ-VAS) were included in the EQ-5D-3L. Furthermore, the EQ-5D time trade-off indexed data were analyzed using both US- and UK-based value sets. In comparison with the CHOP group, the mean baseline score was lower for the BV plus CHP group, and in general trended lower during the study period. In both treatment groups, these scores improved over time. The trends detected in the US-based value set were in line with those in the UK-based set. Using a linear mixed model analysis, change in EQ-5D score from baseline showed that overall, there was no difference between treatment groups based on the US- and UK-based value sets, and the published MID was not reached.

Limitations: Population of the ECHELON-2 trial is broader than the reimbursement request

The population of the ECHELON-2 trial is broader than the reimbursement request in this CADTH submission. Patients with the following histologies were eligible for inclusion into the trial: ALK-positive sALCL with IPI score greater than or equal to two, ALK-negative sALCL, PTCL-NOS, AITL, ATLL, EATL, and hepatosplenic T-cell lymphoma; however, this reimbursement request is for patients with ALK-positive sALCL with an IPI score greater than or equal to two, ALK-negative sALCL, PTCL-NOS, and AITL only. Therefore, the request is for a large subpopulation (ALK-positive sALCL with an IPI score greater than or equal to two, ALK-negative sALCL, PTCL-NOS, and AITL) that was not analyzed separately from the ITT population. While the number of patients with the other disease histologies, that were not part of the reimbursement request was small (n= 10; 5 in each group), the impact of excluding these 10 patients from the results seen in the overall trial population is not known.

All primary and secondary efficacy and safety analyses in ECHELON-2 were assessed regardless of disease subtype. Although the primary and key secondary outcome (OS) were also reported by PTCL subtype,

there is significant uncertainty in these results as the study was not designed to test specific hypotheses for these subgroups. Combining all subgroups into one group, regardless of PTCL subtype, discounts the potential for clinical heterogeneity in disease processes or the potential for differences in prognostic heterogeneity depending upon the specific PTCL subtype.

Subgroup analyses are considered exploratory because the ECHELON-2 trial was not designed to test specific hypotheses for subgroups. The only subgroup for which an alpha-controlled hypothesis test was pre-specified is the subgroup of sALCL patients for PFS. The purpose of the exploratory subgroup analyses is hypothesis generating only.

Safety: Manageable toxicity profile, similar between groups

BV plus CHP was well-tolerated and had a similar safety profile to that of CHOP. Overall, TEAEs of any grade reported in greater than or equal to 10% of patients in the BV plus CHP group (versus the CHOP group) were comparable between the two groups (99% versus 98%, respectively). However, higher rates of TEAEs in the BV plus CHP group versus the CHOP included: nausea (46% versus 38%), diarrhea (38% versus 20%), pyrexia (26% versus 19%), vomiting (26% versus 17%), fatigue (24% versus 20%), and anemia (21% versus 16%).

Grade 3 or higher TEAEs, occurring in greater than or equal to 2% of patients in the BV plus CHP group (versus CHOP), were comparable between both trial groups (66% and 65% in the BV plus CHP and CHOP groups, respectively). The most common Grade 3 or higher AEs included neutropenia (35% versus 34%), febrile neutropenia (18% versus 15%), and anemia (13% versus 10%). A similar percentage of patients experienced severe adverse events (SAEs), 87% in each treatment group. SAEs were reported for greater than or equal to 2% of patients in the BV plus CHP group (versus CHOP) and included febrile neutropenia (14% versus 12%), pneumonia (5% versus 1%), pyrexia (4% versus 3%), neutropenia (4% versus 3%), pneumonitis (2% versus 0), sepsis (2% versus 2%), and diarrhea (2% versus 1%).

Comparable discontinuation rates were reported between both groups of the trial, with a total of 29 patients (6%) having experienced an AE that resulted in treatment discontinuation; 14 patients (6%) in the BV plus CHP group and 15 patients (7%) in the CHOP group.

Similarly, a comparable number of treatment-emergent peripheral neuropathy was reported between the trial groups; 117 patients (52%) in the BV plus CHP group and 124 patients (55%) in the CHOP group. A total of 41 patients (18%) in the BV plus CHP group and 33 patients (15%) in the CHOP group experienced treatment-emergent febrile neutropenia.

Granulocyte-colony stimulating factor (G-CSF) primary prophylaxis was administered to 75 patients (34%) in the BV plus CHP group and 61 patients (27%) in the CHOP group. In both treatment groups, prophylactic treatment reduced the incidence and severity of febrile neutropenia and Grade 3 or higher neutropenia to a similar degree.

A total of 123 deaths had been reported in patients treated in either group, 50 in the BV plus CHP group and 73 in the CHOP group. In the BV plus CHP group, 36 deaths were disease related, 10 were not disease related, and the disease relationship was unknown for four patients. In the CHOP group, 58 deaths were disease related, seven were not disease related, and the disease relationship was unknown for eight patients.

Need and burden of illness: Need for effective treatments that lead to long-term remission and survival and potential cure.

TCL is a rare group of entities accounting for 5% to 10% of all cases with Non-Hodgkin lymphoma (NHL). PTCL is a broad category with several heterogeneous subtypes including PTCL-NOS, sALCL and AITL that account for almost 70% of all cases with PTCL. Canadian Cancer Statistics (2019) expected approximately 10,000 new cases of NHL per year. Assuming approximately 7% of these cases were T-cell NHL, there would have been approximately 700 new cases of TCL with an age-standardized incidence rate of 1.7 cases per 100,000. Of these, about 80% (560 patients) would have been part of PTCL-NOS, sALCL, or AITL subtypes.

Current Canadian standard of care of patients with PTCL is either CHOP or CHEOP with or without autologous SCT consolidation. In general, treatment outcomes have been poor with conventional chemotherapy regimens. In a Canadian series, five-year OS for PTCL-NOS, AITL, ALK-positive sALCL and

ALK-negative sALCL was 35%, 36%, 58%, and 34% (Savage et al., 2004). According to the CGP patients with PTCL have an unmet need for effective treatment options that lead to long-term remission and survival and to a potential cure.

Registered clinician input: ECHELON-2 demonstrated significant improvements in PFS and OS in favour of BV plus CHP; BV plus CHP would be used in first-line treatment of PTCL patients.

Two clinician inputs (one joint and one individual input) were provided for this submission. Clinicians found that BV plus CHP provided benefit with regard to PFS and OS in eligible PTCL patients, and that the eligibility criteria from the study are representative of the population seen in clinical practice. They believe that more data would be required for use outside of this population. BV plus CHP would be used as a first-line treatment in PTCL patients, where there is currently a substantial unmet medical need. The companion testing for CD30 expression is routinely tested and is available for pathological assessment.

PATIENT-BASED VALUES

Values of patients with PTCL: longer survival, longer remission, better QoL, and fewer side effects.

One patient advocacy group provided input for this submission. From a patient's perspective the symptoms of PTCL that most commonly affected their QoL were fatigue or lack of energy, followed by fevers and then enlarged lymph nodes. Patients noted that nausea/vomiting and mouth sores were the most difficult side effects to tolerate of current treatment. They also reported that fatigue and activity levels were most significantly impacted by their treatment.

In terms of patients' values and expectations when it comes to new therapies for their disease, all respondents rated having choice in deciding which drug to take based on known side effects and expected outcomes of treatment as extremely important. The majority of respondents were willing to tolerate significant side effects from new drug therapies. The patient advocacy group reported that when it comes to the importance of various outcomes for a new drug or treatment for PTCL, patients prioritize longer survival, longer remission, better QoL, and fewer side effects.

Patient values on treatment: overall well-tolerated, impact on fatigue and activity levels

In total, two patient respondents indicated having experience with BV plus CHP. Overall BV plus CHP was well-tolerated and respondents reported that the most difficult side effect to tolerate was fatigue, which worsened throughout treatment. Both respondents reported the following side effects: fatigue, hair loss, mouth sores, and neutropenia. One respondent reported experiencing: infections, diarrhea, infusion reaction, tingling or numbness (peripheral neuropathy), breathing difficulties, and/or constipation. One respondent noted that an infusion reaction caused some distress, but that it only happened one time. Treatment with BV plus CHP was reported to impact the following aspects of quality of life: treatment-related fatigue, activity level, treatment tolerance, infusion time, number of clinic visits, number of infections, and frequency of infections.

ECONOMIC EVALUATION

BV is available as 50 mg vials. The recommended dose of BV is 1.8 mg/kg every three weeks plus CHP. At the sponsor's submitted price of $4,840 per vial, the cost per dose of BV for a 74.4 kg patient (as per the ECHELON-2 baseline characteristics) is $14,520. The cost per course ranges between $87,120 and $116,160 for six to eight cycles of treatment.

The sponsor submitted a partitioned survival analysis comparing BV plus CHP with CHOP for previously untreated adult patients with sALCL, PTCL-NOS, or AITL whose tumours express cluster of differentiation 30 (CD30). The sponsor undertook a scenario analyses that also considered CHOEP as a comparator. The economic analysis was undertaken over a lifetime (45 years) time horizon from the perspective of the public health-care payer. The proportion of patients who were progression-free, experienced PD, or were dead at any time over the model time horizon was derived from non-mutually exclusive survival curves. The clinical efficacy of BV plus CHP and CHOP was sourced from ECHELON-2 trial. Patients with ATLL or EATL subtypes in the ECHELON-2 trial were removed from the analysis, and only the subset of patients with sALCL, PTCL-NOS or AITL were included, as per the funding indication. Different parametric models were fitted to the trial data to extrapolate treatment effect beyond observed data. The sponsor assumed

the treatment effect associated with SCT and subsequent treatment was implicitly incorporated when applying the PFS and OS outcomes from the trial.

The sponsor reported a probabilistic ICER of $32,470 per quality-adjusted life-year (QALY) gained for BV plus CHP versus CHOP, and an ICER of $27,859 per QALY gained for BV plus CHP versus CHOEP.

CADTH identified the following key limitations of the sponsor's submitted economic analysis:

- The sponsor omitted CHOEP as a comparator in its base-case analysis. They did, however, include it as a scenario analysis on request.
- The patient populations were heterogeneous in terms of histological subtypes resulting in survival differences across subtypes, which are expected to have an impact on the cost-effectiveness of BV plus CHP. The sponsor's submission did not allow stratification by histological subtype, but provided a separate model for the sALCL subtype at the request of CADTH. The cost-effectiveness for patients with PTCL-NOS subtype and AITL subtypes is unknown.
- There was significant uncertainty regarding long-term extrapolation as OS data were not mature and short-term data (median follow-up of 36 months) were used to extrapolate long-term benefits throughout the lifetime horizon (i.e., 45 years), resulting in an increased risk for an overestimation of patient survival. Furthermore, as long-term OS extrapolations resulted in survival higher than the general population, the sponsor replaced extrapolated OS with general population survival rates. The assumption that survival in these patients would at some point reach that of the general population was felt to be unrealistic by the CGP.
- Health utility values used in the sponsor's model were based on the EQ-5D from the ECHELON-2 trial. The sponsor used US weights (value set) in the analysis, and as such utility values may not reflect the preferences of Canadian patients. Furthermore, utility values are likely overestimated as values for the progression-free state are very close to the value estimated in the general population of healthy Canadians.
- Treatment-specific disutilities for AEs were not included in the sponsor's base case. AE disutilities for Grade 3 and 4 AEs were included in a scenario analysis, excluding AEs considered clinically meaningful to clinical experts and patient groups consulted by CADTH.
- The sponsor's model structure did not explicitly consider SCT. Since patients undergoing SCT may have longer survival than patients without SCT, SCT should have been modelled separately in order to assess the impact of varying SCT rates on the overall cost-effectiveness of BV plus CHP.

To account for the above limitations, CADTH considered: the inclusion of CHOEP as comparator (assuming the same efficacy as CHOP), alternative long-term extrapolations, inclusion of increased non-cancer mortality, the use of a UK value set applied to EQ-5D data collected during the ECHELON-2 trial, the inclusion of AE-specific disutilities, and a revised time horizon of 42 years (i.e., until the cohort reaches 100 years old). CADTH estimated that the ICER of BV plus CHP compared to CHOP is $79,319 per QALY gained, whereas the ICER of BV plus CHP compared to CHOEP is $72,991 per QALY gained. Price reductions of 30% to 35% would bring the ICER to approximately $50,000 per QALY.

Some identified limitations could not be addressed by CADTH, such as the impact of a different proportion of patients undergoing consolidative SCT and the impact of Grade 1 and 2 AEs relevant to patients. The sponsor provided a separate model for the sALCL subtype at CADTH's request. However, the model provided by the sponsor for this subtype was different from the model provided for the overall population, and as such CADTH was unable to perform all reanalyses in line with the CADTH base case.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: submitted budget impact analysis is underestimated

CADTH noted that the key factors influencing the incremental budget impact include the number of cycles of BV plus CHP, the proportion of NHL that is PTCL, and the market shares of BV plus CHP. CADTH identified several limitations in the submitted budget impact analysis that may have led to an underestimation of the total budget impact of BV plus CHP. Changes made by CADTH included the use of Ontario costs for comparators, the use of updated incidence data, the inclusion of prophylaxis costs, and the use of updated market shares.

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee

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

pERC Membership During Deliberation of the Initial Recommendation

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice-Chair)
Daryl Bell, Patient Member
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Michael Crump, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Dr. Christian Kollmannsberger, Oncologist
Dr. Christopher Longo, Health Economist
Cameron Lane, Patient Member
Valerie McDonald, Patient Member
Dr. Marianne Taylor, Oncologist
Dr. W. Dominika Wranik, Health Economist

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

- Dr. Avram Denburg who was not present for the meeting
- Dr. Christopher Longo who was not present for the discussion and deliberation for this review
- Dr. Maureen Trudeau who did not vote due to her role as the pERC Chair.

pERC Membership During Deliberation of the Final Recommendation

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice-Chair)
Daryl Bell, Patient Member
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Michael Crump, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Dr. Christian Kollmannsberger, Oncologist
Dr. Christopher Longo, Health Economist
Cameron Lane, Patient Member
Valerie McDonald, Patient Member
Dr. Marianne Taylor, Oncologist
Dr. W. Dominika Wranik, Health Economist

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

- Dr. Maureen Trudeau, who did not vote due to her role as the pERC chair.

Avoidance of conflicts of interest

All members of pERC must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of BV for PTCL, through their declarations, no members had a real, potential, or perceived conflict, and based on application of the *pCODR Conflict of Interest Guidelines*, none of the members were excluded from voting.

Information sources used

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

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in this Recommendation document.

Use of this Recommendation

This Recommendation from pERC is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policy-makers make well-informed decisions and improve the

quality of health care services. While patients and others may use this Recommendation, it is for informational and educational purposes only, and should not be used as a substitute for the application of clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

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

PAG Implementation Questions	pERC Recommendation
• PAG is seeking guidance on the use of BV plus other chemotherapy regimens than CHP.	• Although the ECHELON-2 trial did not evaluate BV in combination with cyclophosphamide, etoposide, and prednisone, pERC agreed with the CGP that the results of the trial can be generalized to BV in combination with cyclophosphamide, etoposide, and prednisone. Most clinicians would consider CHP and the combination of cyclophosphamide, etoposide, and prednisone as interchangeable in the management of PTCL.
• PAG noted that there is a potential for indication creep with BV for second-line or later lines of treatment for patients who have relapsed/refractory PTCL following initial frontline treatment.	• pERC agreed with the CGP that there is currently insufficient evidence to use BV plus CHP retreatment in patients who relapse following BV plus CHP. There is also insufficient evidence regarding the efficacy of BV plus other drugs in the relapsed/refractory setting.
• PAG is seeking guidance on the appropriateness of retreatment with single agent BV for sALCL or other CD30+ PTCL who receive frontline BV plus CHP. If appropriate, what would be the time frame from completion of first-line treatment to relapse?	• pERC was uncertain of an appropriate time frame for retreatment with a single drug BV as there is insufficient evidence to guide retreatment with BV; however, pERC noted that the CGP suggested a 6-month time frame from completion of first-line treatment to relapse with single agent BV.
• PAG noted that PTCL is a heterogeneous group of aggressive lymphomas with many subtypes. It will be important to clearly specify which subtypes of PTCL are eligible for treatment with BV.	• The subgroup analysis of PFS by the sALCL histologic subtype was the only subgroup for which an alpha-controlled hypothesis test was pre-specified in the ECHELON-2 trial. pERC agreed with the CGP it would be reasonable to extend treatment with BV plus CHP to the PTCL-NOS and AITL subtypes given the subgroup results for OS were consistent with the overall study results, both PTCL-NOS and AITL are nodal PTCL similar to sALCL, due to the rarity of these subtypes with CD30-expressing tumours, RCTs will likely not be feasible, safety profile was similar across all subgroups included in ECHELON-2 trial, and CD30-expression is the target for the mechanism of action of BV. • pERC felt it would be reasonable to extend treatment with BV plus CHP to other subtypes i.e., ATLL and EATL on a case-by-case basis. While pERC acknowledged the small sample size of the ATLL and EATL subgroups in the ECHELON-2 trial, pERC agreed that it may be reasonable to generalize the trial results to patients with ATLL and EATL, as these patients were included in the ITT analyses, it is unlikely that there will be trials specifically designed for this small group of patients, and there is no apparent biological rationale to assume that outcomes of BV plus CHP therapy would be different between subtypes of CD30-positive PTCL. • pERC agreed that there is currently insufficient evidence to make an informed recommendation on the use of BV plus CHP in patients with ALK-positive sALCL who have a low IPI score (IPI score < 2). Therefore, the Committee noted that a separate submission to CADTH for BV plus CHP in patients with ALK-positive sALCL and low IPI score, would be required.

• PAG noted that additional resources (e.g., nursing and clinic visits) are required to monitor and treat infusion-related reactions and AEs (e.g., diarrhea, neutropenia/febrile neutropenia, and peripheral neuropathy) as well as monitor complete blood count.	• pERC agreed with the CGP that it is not anticipated that additional health care resources will be required (beyond those that are typically required for comparator treatments) to monitor and treat toxicities.
• PAG noted that 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.	• Administration of G-CSF is considered standard of care in Canadian practice in selected patients. The use of G-CSF in clinical practice is physician dependent and criteria vary across provinces (e.g., in Manitoba, patients > 65 years and with multiple comorbidities qualify for G-SCF). The trial results are generalizable to the Canadian patient population.

AE = adverse event; AITL = angioimmunoblastic T-cell lymphoma; ALK = anaplastic lymphoma kinase; BV = brentuximab vedotin; CGP = Clinical Guidance Panel; CHP = cyclophosphamide, doxorubicin, and prednisone; EATL = enteropathy-associated T-cell lymphoma; G-CSF = granulocyte-colony stimulating factor; ITT = intention to treat; IPI = International Prognostic Index; OS = overall survival; PFS = progression-free survival; pERC = CADTH pan-Canadian Oncology Drug Review Expert Review Committee; PTCL = peripheral T-cell lymphoma; PTCL-NOS = peripheral T-cell lymphoma not otherwise specified; RCT = randomized controlled trial; sALCL = systemic anaplastic large-cell lymphoma.