CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Brentuximab Vedotin (Adcetris) for Peripheral T-cell Lymphoma

June 4, 2020

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List of Abbreviations

AE	adverse event
AITL	angioimmunoblastic T-cell lymphoma
ALK	anaplastic lymphoma kinase
ATLL	adult T-cell leukemia/lymphoma
ASCO	American Society of Clinical Oncology
BICR	blinded independent central review
BV	brentuximab vedotin
C	cyclophosphamide
CGP	Clinical Guidance Panel
CHP	cyclophosphamide, doxorubicin and prednisone
CHOEP	cyclophosphamide, doxorubicin, vincristine, etopside and prednisone
CHOP	cyclophosphamide, doxorubicin, vincristine and prednisone
CI	confidence interval
CR	complete remission
CRR	complete remission rate
DB	double-blind
E	etoposide
EATL	enteropathy-associated T-cell lymphoma
ECOG	Eastern Cooperative Oncology Group
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EOT	end of treatment
ESMO	European Society of Medical Oncology
G-CSF	granulocyte-colony stimulating factor
H	doxorubicin
HR	hazard ratio
HRQOL	health-related quality of life
IPI	International Prognostic Index
IRF	Independent review facility
ITT	intention-to-treat
IV	intravenous
MRU	medical resource utilization
NOS	not otherwise specified
NR	not reported
O	vincristine
OS	overall survival
ORR	objective response rate
P	prednisone
pCODR	pan-Canadian Oncology Drug Review
PD	progressive disease
pERC	pCODR Expert Review Committee
PFS	progression free survival
PTCL	peripheral T-cell lymphoma
Pts	patients
QOL	quality of life
RCT	randomized controlled trials
sALCL	systemic anaplastic large cell lymphoma
SCT	stem cell transplantation
SD	standard deviation

SAE	severe adverse events
TEAE	treatment-emergent adverse event
TRAE	treatment-related adverse event
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 regarding brentuximab vedotin (Adcetris) for peripheral T-cell lymphoma (PTCL). 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 regarding brentuximab vedotin (Adcetris) for PTCL conducted by the Lymphoma Clinical Guidance Panel (CGP) and the pCODR 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 on brentuximab vedotin (Adcetris) for PTCL, a summary of submitted Provincial Advisory Group Input on brentuximab vedotin (Adcetris) for PTCL, and a summary of submitted Registered Clinician Input on brentuximab vedotin (Adcetris) for PTCL, and 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 in combination with cyclophosphamide (C), doxorubicin (H), and prednisone (P; CHP) compared to combination chemotherapy with cyclophosphamide, doxorubicin, vincristine (O), and prednisone (CHOP) or CHOP-like regimens with curative intent 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.

Health Canada has issued a marketing authorization, without conditions, for brentuximab vedotin 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, in combination with cyclophosphamide, doxorubicin, and prednisone (CHP). The Health Canada indication aligns with the pCODR 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 1.8 mg/kg to a maximum of 180 mg in combination with CHP administered every 3 weeks for 6 or 8 cycles, or until disease progression or unacceptable toxicity. Brentuximab vedotin is administered as an intravenous infusion over 30 minutes.[1]

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

One randomized controlled trial was identified that met the eligibility criteria of the systematic review.[2] ECHELON-2 was a randomized, double-blind, double-dummy, placebo-controlled, active comparator, multicenter, phase 3 clinical trial designed to evaluate the efficacy and safety of including brentuximab vedotin (BV) in the treatment of patients with previously untreated, CD30-positive, peripheral T-cell lymphoma (PTCL).[2] Eligible patients from 132 study sites in 17 countries (four Canadian sites [3]) were included in the trial.[2]

The trial randomized 452 patients in a 1:1 manner to receive 6 to 8, 21-day cycles of treatment. A total of 226 patients received BV + cyclophosphamide, doxorubicin, placebo for vincristine, and prednisone (CHP) and 226 patients received cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP), and placebo for BV.[2] Eligible patients had previously untreated, CD30-positive PTCL with an Eastern Cooperative Oncology Group (ECOG) performance status ≤2 and one of the following eligible histologies; anaplastic lymphoma kinase (ALK)-positive systemic anaplastic large cell lymphoma (sALCL) with an International Prognostic Index (IPI) ≥2, ALK-negative sALCL, PTCL-not otherwise specified (NOS), angioimmunoblastic T-cell lymphoma (AITL), adult T-cell leukemia/lymphoma (ATLL), enteropathy-associated T-cell lymphoma (EATL), or hepatosplenic T-cell lymphoma. Randomization was stratified by ALK-positive sALCL versus all other histologic subtypes and IPI score (0-1 versus 2-3 versus 4-5).[2]

The primary outcome of the trial was progression-free survival (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 progressive disease (PD), death due to any cause, or receipt of subsequent anticancer chemotherapy to treat residual or progressive disease, whichever occurred first.[2] Receipt of post-treatment consolidative radiotherapy, post-treatment chemotherapy for the purpose of mobilizing peripheral stem cells, or consolidative autologous or allogeneic stem cell transplantation (SCT) was not considered disease progression or as having started new anticancer therapy.[4] Key secondary outcomes included PFS per IRF in the subset of patients with sALCL, complete remission (CR) rate per IRF following completion of study treatment, overall survival (OS), objective response rate (ORR) per IRF following completion of study treatment, safety, and quality of life (QOL).[2]

Overall, 449 of the 452 randomized patients received their allocated treatment.[2] Three patients randomized to the BV+CHP group did not receive treatment. A total of 370 patients (82%) have completed treatment; 192 (85%) on the BV+CHP group and 178 (79%) on the CHOP group.[5] As of the August 15, 2018 cut-off date for the primary efficacy analysis, at a median duration of follow-up of 36.2 months (95% CI, 35.9-41.8)[2], 296 (65%) patients remained in long-term follow-up; 157 (69%) on the BV+CHP group and 139 (62%) on the CHOP group.[6]

The baseline patient demographics and characteristics were well balanced between the two treatment groups.[2] The greatest proportion of patients (28%) came from the United States and were white (62%) males (63%). The median age was 58 years, with 69% of patients under the age of 65.[6] Most patients had an ECOG Performance Status (PS) of 0 (39%) or 1 (39%). A total of 316/452 (70%) patients had a diagnosis of sALCL per local assessment. Of the 316 patients with sALCL, 218 (48% of the total population of randomized patients) were ALK-negative and 98 (22%) were ALK-positive. The remaining 30% of patients had diagnoses of PTCL-NOS (16%), AITL (12%), ATLL (2%), EATL (1%). The majority of patients had Stage III (27%) or IV (53%) disease. The median time from diagnosis to the first dose of study treatment was 0.9 months (range, 0-19 months) across both treatment groups. The median percent CD30-positive cells per local assessment and central review was 90% and 95%, respectively.[2]

Highlights of the key outcomes of the ECHELON-2 trial are outlined in Table 1.1.

Table 1.1 Highlights of key outcomes in the included ECHELON-2 trial.[2]

Trial Outcomes	ECHELON-2	
	BV+CHP (N=226)	CHOP (N=226)
Primary data source	**Horwitz et al. Lancet 2018**	
Data cut-off date	**August 15, 2018**	
Median duration of follow-up in months	**36.2**	
Primary Outcome, PFS per blinded IRF		
No. PFS events (%)	95 (42%)	124 (55%)
HR (95%CI)	0.71 (0.54-0.93)	
p-value	0.0110	
Median PFS, months (95% CI)	48.2 (35.2- not evaluable)	20.8 (12.7-47.6)
Key Secondary Outcomes		
PFS among sALCL subgroup		
HR (95% CI)	0.59 (0.42-0.84)	
p-value	0.0031	
OS		
No. deaths (%)	51 (23%)	73 (32%)
HR (95%CI)	0.66 (0.46-0.95)	
p-value	0.0244	
Median OS, months (95% CI)	Not reached	Not reached
CRR		
Response rate difference (95% CI)	11.9 (3.1-20.8)	
p-value	0.0066	
ORR		
Response rate difference (95% CI)	11.1 (3.4-18.7)	
p-value	0.0032	
QOL		
QOL was measured using the EORTC Core Quality of Life Questionnaire – Core 30 (QLQ-C30), the FACT/GOG-NTX subscale, and the European Quality of Life 5-Dimensions Questionnaire (EQ-5D-3L). Patient compliance with the questionnaires was high (>90%) and similar in both treatment groups. Except for the difference in scores between the treatment groups (in favor of CHOP) for diarrhea at Cycle 7, none of the differences in patient-reported outcomes including the Neurotoxicity for the FACT/GOG-NTX were clinically meaningful based on the published MCIDs.		
Harms Outcome, n (%)	**BV+CHP (N=223)**	**CHOP (N=226)**
Grade ≥3	147 (66)	146 (65)
Any SAE	87 (39)	87 (38)
Any TEAE[a]	221 (99)	221 (98)
Any TRAE[b]	201 (90)	193 (85)
WDAE	14 (6)	15 (7)
AEs resulting in death	8 (4)	16 (7)

Notes: [a] – TEAEs are defined as newly occurring (not present at baseline) or worsening after first dose of BV or any component of multiagent chemotherapy (CHP or CHOP)
Abbreviations: AE - adverse event; BV – brentuximab vedotin; CI - confidence interval; CRR – complete remission rate; HR - hazard ratio; HRQOL - health-related quality of life; IRF – independent review facility; NR - not reported; ORR – objective response rate; PFS – progression-free survival; QOL – quality of life; SD - standard deviation; SAE – serious adverse event; TEAE - treatment-emergent adverse event; TRAE – treatment-related adverse event; WDAE - withdrawal due to adverse event
*HR < 1 favours [BV+CHP]

Treatment with BV+CHP resulted in a statistically significant improvement in PFS per blinded IRF in the intention-to-treat (ITT) population compared to CHOP.[2] Patients treated with BV+CHP had a 29% reduction in the risk of a PFS event compared with patients treated with CHOP (stratified HR 0.71; 95% CI 0.54-0.93, p=0.011). The median PFS for the BV+CHP and CHOP groups was 48.2 months and 20.8 months, respectively.[2] Treatment with BV+CHP was also superior to treatment with CHOP for all key secondary outcomes including: 1) PFS per IRF in the subgroup

of patients with sALCL (the stratified HR was 0.59, 95% CI 0.42-0.84, p=0.0031, which equates to a 41% reduction in the risk of a PFS event for patients treated with BV+CHP versus CHOP); 2) the CR rate was significantly higher in the BV+CHP group versus CHOP (68% versus 56%, respectively); 3) there were significantly fewer deaths in the BV+CHP group versus the CHOP group (stratified HR 0.66, 95% CI 0.46-0.95, p=0.0244; and 4) the ORR at end of treatment (EOT) was significantly higher with BV+CHP versus CHOP (Table 1.1).[2]

BV+CHP was well tolerated and had a similar safety profile to that of CHOP.[2] Overall, treatment-emergent adverse events (TEAE) of any grade reported in ≥10% of patients in the BV+CHP group (versus the CHOP group) were comparable between the two groups (99% versus 98%, respectively). However, higher rates of TEAEs in the BV+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%).[2] Grade 3 or higher TEAEs, occurring in ≥2% of subjects in the BV+CHP group (versus CHOP), were comparable between both trial groups (66% and 65% in the BV+CHP and CHOP groups, respectively). The most common Grade 3 of higher AEs included neutropenia (35% versus 34%), febrile neutropenia (18% versus 15%), and anemia (13% versus 10%).[4] A similar percentage of patients experienced severe adverse events (SAEs), 87% in each treatment group.[4] SAEs reported for ≥2% of patients in the BV+CHP group (versus CHOP) were 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%).[4] Comparable discontinuation rates were reported between both groups of the trial, with a total of 29 patients (6%) having experienced an adverse event that resulted in treatment discontinuation; 14 patients (6%) in the BV+CHP group and 15 patients (7%) in the CHOP group.[2] Similarly, a comparable number of treatment-emergent peripheral neuropathy (PN) was reported between the trial groups; 117 patients (52%) in the BV+CHP group and 124 patients (55%) in the CHOP group. A total of 41 patients (18%) in the BV+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+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. As of the August 15, 2018 data cut-off date, a total of 123 deaths had been reported in patients treated on either group, 50 in the BV+CHP group and 73 in the CHOP group.[4] In the BV+CHP group, 36 deaths were disease related, 10 were not disease related, and the disease relationship was unknown for 4 patients. In the CHOP group, 58 deaths were disease related, 7 were not disease related, and the disease relationship was unknown for 8 patients.[4]

Limitations

- Overall, the ECHELON-2 trial was well-conducted using sound methodological and statistical principles that were outlined a priori. Several techniques such as central randomization, allocation concealment, and blinding at various levels were employed to reduce the possibility of bias. Study outcomes were well- and appropriately defined and measured using standardized and internationally accepted criteria and performed on the ITT population.
- 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+ sALCL with IPI score ≥2, ALK- sALCL, PTCL NOS, AITL, ATLL, EATL, and hepatosplenic TCL; however, this reimbursement request is for patients with: ALK+ sALCL with IPI score ≥2, ALK- sALCL, PTCL NOS, and AITL only. Therefore, the request is for a large subpopulation (ALK+ sALCL with IPI score ≥2, ALK- 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 sub-type. Although the primary and key secondary outcome (OS) were also reported by PTCL sub-type, there is significant uncertainty in these results as the study was not designed to test specific hypotheses for these subgroups.[3] Combining all subgroups into one group, regardless of PTCL sub-type, discounts the potential for clinical heterogeneity in disease processes or the potential for differences in prognostic heterogeneity depending upon the specific PTCL sub-type.[7] The subgroup analysis of sALCL for PFS was the only subgroup for which an alpha controlled hypothesis test was pre-specified.[3]
- While significant effort was made to reduce the probability of bias in the ECHELON—2 trial, the possibility of sponsorship bias remains. The majority of contributors to the study design, maintenance of study quality, data analysis, and the study report received personal or professional funds from the study sponsor.[2] Such conflicts of interest do raise some concerns.[8]
- HRQoL outcomes were exploratory endpoints. The ECHELON-2 trial was not designed to test specific hypotheses for HRQoL outcomes and no firm conclusions can be drawn from these results.
- Overall, ECHELON-2 was a well-conducted trial in which numerous precautions were taken to minimize the risk of many forms of bias commonly encountered in randomized controlled trials. Despite the limitations outlined, one can be reasonably confident that the overall effect of significant improvement in PFS is due to the study intervention, brentuximab vedotin.

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

The following patient advocacy group(s) provided input on Brentuximab-Vedotin (Adcetris) for the frontline treatment of patients with CD30-expressing Peripheral T Cell Lymphoma (PTCL), in combination with cyclophosphamide, doxorubicin, and prednisone (CHP) and their input is summarized below: Lymphoma Canada (LC).

From a patient's perspective the symptoms of PTCL that most commonly affected their quality of life 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, respondents all 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. LC 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 and disease control.

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

Economic factors:

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

Registered Clinician Input

The registered clinicians(s) provided input on Brentuximab-vedotin (BV) (Adcetris) for the frontline treatment of patients with CD30-expressing Peripheral T Cell Lymphoma (PTCL), in combination with cyclophosphamide, doxorubicin, and prednisone (CHP) and their input is summarized below: Two registered clinician input submissions were provided, representing a total of six clinicians. One joint input submission on behalf of five clinicians from British Columbia Cancer (BCC) as well as an individual input by a single hematologist from Cancer Care Ontario Hematology DAC.

Clinicians found that BV in combination with CHP (BV+CHP) provided benefit with regards to progression-free survival (PFS) and overall survival (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+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.

Summary of Supplemental Questions

There were no supplemental questions identified for this review.

Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR 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 1.2 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 1.2: Assessment of generalizability of evidence for brentuximab vedotin in PTCL.

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence from ECHELON-2 trial</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td rowspan="3">Population</td><td>PTCL sub-type</td><td>
<table>
<tr><th>Subtypes</th><th>BV+CHP (n=226)</th><th>CHOP (n=226)</th></tr>
<tr><td>sALCL

ALK +
ALK -</td><td>162 (72%)

49 (22%)
113 (50%)</td><td>154 (68%)

49 (22%)
105 (46%)</td></tr>
<tr><td>PTCL-NOS</td><td>29 (13%)</td><td>43 (19%)</td></tr>
<tr><td>AITL</td><td>30 (13%)</td><td>24 (11%)</td></tr>
<tr><td>ATLL</td><td>4(2%)</td><td>3 (1%)</td></tr>
<tr><td>EATL</td><td>1 (0%)</td><td>2 (1%)</td></tr>
</table>
The subgroup analyses are considered exploratory because the study was not designed to test specific hypotheses for these subgroups. The only subgroup for which an alpha controlled hypothesis test was prespecified was the subgroup of sALCL patients.
PFS results as per IRF for the sALCL subgroup: HR 0.59, 95% CI 0.42-0.84; p=0.0031.</td><td>Are the overall trial results generalizable to patients across all PTCL sub-types? Are there differences in clinical and prognostic factors with specific PCTL sub-types that could affect the interpretation of the trial results? If so, what factors are these?</td><td>The only subgroup for which an alpha controlled hypothesis test was prespecified was the subgroup of sALCL patients.
The CGP supports generalizing the study results to two exploratory subgroups (i.e., PTCL-NOS, and AITL). The CGP agreed that this generalization is reasonable, as (i) the subgroup results for OS were consistent with the overall study results, (ii) both (PTCL-NOS and AITL) are nodal PTCL similar to sALCL, (iii) due to the rarity of these subtypes with CD30-expressing tumours, RCTs will likely not be feasible, (iv) safety profile was similar across all subgroups, and (v) CD30-expression is the target for the mechanism of action of brentuximab.
The CGP agreed that the data for the ATLL and EATL exploratory subgroups from the ECHELON-2 trial was insufficient to draw meaningful conclusions on the treatment effect of brentuximab plus CHP.</td></tr>
<tr><td>Stage of disease</td><td>Most patients had Stage IV disease.
Stage I: n=21/452 (5%)
Stage II: n=67/452 (15%)
Stage III: n=124/452 (27%)
Stage IV: n=240/452 (53%)</td><td>Does stage limit the interpretation of the trial results with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?</td><td>The trial population in terms of their stage of disease at presentation is reflective of patients in Canadian clinical practice. Therefore, the stage of disease does not limit the interpretation of the trial results in the Canadian context.</td></tr>
<tr><td>ECOG PS</td><td>Only patients with ECOG PS ≤2 were included.
ECOG 0: n=177/452 (39%)
ECOG 1: n=176/452 (39%)
ECOG 2: n=98/452 (22%)</td><td>Are the trial results generalizable to patients with an ECOG score of Grade 3 or higher?</td><td>The CGP agreed that it would be appropriate to treat patients with ECOG PS of 3 or greater with brentuximab plus CHP at the desecration of the treating physician. Situations in which the patients' poor performance status (i.e., 3 or greater) is affected by the underlying disease, treating physicians may decide to offer brentuximab plus CHP.</td></tr>
</table>

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence from ECHELON-2 trial</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td></td><td>International Prognostic Index (IPI)</td><td>Patients were stratified according to baseline IPI score (0-1, versus 2-3, versus 4-5). Eligible histologies included ALK+ sALCL with IPI score ≥2.

<table><tr><th>Baseline IPI score</th><th>BV+CHP</th><th>CHOP</th></tr><tr><td>0</td><td>8 (4%)</td><td>16 (7%)</td></tr><tr><td>1</td><td>45 (20%)</td><td>32 (14%)</td></tr><tr><td>2</td><td>74 (33%)</td><td>78 (35%)</td></tr><tr><td>3</td><td>66 (29%)</td><td>66 (29%)</td></tr><tr><td>4</td><td>29 (13%)</td><td>25 (11%)</td></tr><tr><td>5</td><td>4 (2%)</td><td>9 (4%)</td></tr></table></td><td>Does the IPI score limit the interpretation of the trial results with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?</td><td>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 or greater than 2. As patients with ALK-positive sALCL with an IPI score of less than 2 were excluded from the trial, there is no data to support the generalizability of treatment benefit in this patient population.
The four risk scores (low risk = 0 or 1; low intermediate risk = 2; high intermediate risk = 3; high risk = 4 or 5) of the IPI appear to predict the survival outcome of PTCL patients.[9-11] The IPI score is utilized in clinical practice in determining the prognosis for individual patients.</td></tr>
<tr><td></td><td>Organ dysfunction</td><td>The following required baseline laboratory data:
● bilirubin ≤1.5X upper limit of normal (ULN) or ≤3X ULN for patients with Gilbert’s disease or documented hepatic involvement with lymphoma
● alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3X ULN or ≤5X ULN for patients with document hepatic involvement with lymphoma
● serum creatinine ≤2X ULN</td><td>Does the exclusion of patients with organ dysfunction limit the interpretation of the trial results with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?</td><td>Given the generally well tolerated safety profile of brentuximab + CHP, the CGP suggests it is up to the discretion of the treating physician to apply some flexibility in terms of using brentuximab + CHP in patients with slightly lower lab parameters than those outlined in the ECHELON-2 trial.</td></tr>
<tr><td></td><td>CNS Metastases</td><td>Patients with cerebral/meningeal disease related to the underlying malignancy were excluded.</td><td>Does the presence of cerebral/meningeal disease related to the underlying malignancy limit the interpretation of the trial results with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?</td><td>As patients with cerebral/meningeal disease related to the underlying malignancy were excluded from the trial, there is no data to support the generalizability of treatment benefit to patients with CNS involvement.</td></tr>
</table>

Domain	Factor	Evidence from ECHELON-2 trial	Generalizability Question	CGP Assessment of Generalizability
	Biomarkers	Eligibility was limited to patients with newly diagnosed CD30-positive PTCL. Newly diagnosed, CD30-positive mature T-cell lymphomas. CD30 positivity was defined when the following criteria were met: (i) CD30 detected in ≥10% of neoplastic cells (in cases where enumeration of neoplastic cells is not possible, total lymphocytes may be used), (ii) CD30 staining at any intensity above background, and (iii) membranous, cytoplasmic, and/or golgi pattern of expression of the CD30 antigen.	Is the biomarker an effect modifier (i.e., differences in effect based on biomarker status)? Are the results of the trial applicable to all subgroups equally? Is there a substantial group of patients excluded from the trial to whom the results could be generalized?	As patients who are CD30 negative were excluded from the trial, there is no data to support the generalizability of treatment benefit in this patient population.
	Dose and Schedule	BV: 1.8mg/kg IV on Day 1 of every 21-day cycle by IV infusion (approximately 30 minutes). 1.8 mg/kg up to a maximum of 180 mg Patients received treatments for six to eight 21-day cycles, or until disease progression or unacceptable toxicity. The number of cycles (six or eight) was decided at the investigator's discretion at registration. The median number of treatment cycles per patient was 6.0 (min: 1, max: 8)) for BV+CHP and 6.0 (min: 1, max: 8) for the CHOP group.	Is the trial dosage generalizable to patients in Ontario? Across Canada?	The CGP agreed that the dose used in the trial reflects the standard dose schedule used in Canada and that which has been approved by Health Canada. A target of 8 cycles of study treatment will be administered at the discretion of the treating physician based on patient-specific characteristics, including stage of disease and IPI risk score.
Intervention	**Brentuximab in combination with chemotherapy**	According to the ECHELON-2 trial, brentuximab was combined with cyclophosphamide, doxorubicin, and prednisone (CHP).	Are the overall trial results generalizable to patients who receive brentuximab in combination with other chemotherapy regimens, e.g., CEP (cyclophosphamide, etoposide, and prednisone)	Although the ECHELON-2 trial did not evaluate brentuximab in combination with CEP (cyclophosphamide, etoposide, prednisone) the CGP agreed that the results of the trial can be generalized to brentuximab in combination with CEP. Most clinicians would consider CHP and CEP as interchangeable in the management of PTCL. Clinicians may choose to combine brentuximab with CEP rather than CHP in cases where patients cannot have doxorubicin due to cardiac dysfunction.

Domain	Factor	Evidence from ECHELON-2 trial	Generalizability Question	CGP Assessment of Generalizability
	Treatment Intent	The intent of treatment in the trial was curative.	Are the results of the treatment generalizable to an alternative treatment intent? (i.e., if the trial is palliative in intent, could the therapy also be used in the adjuvant setting or vice versa?)	The CGP agreed that the goal of initial therapy for PTCL is long-term remission or cure.
Comparator	**Use of CHOP as the comparator**	The comparator in the ECHELON-2 trial was CHOP. CHOP was administrated according to the following schedule: C: 750mg/m^2 IV on Day 1 H: 50mg/m^2 IV on Day 1 O: 1.4mg/m^2 (dose capped at 2mg) IV on Day 1 P: 100mg po daily on Days 1-5 (±1 day) PAG and the CGP agreed that currently funded treatments for the present target population are CHOP or CHOP plus etoposide (CHOEP). In order to assess the comparative efficacy of Brentuximab Vedotin plus CHP compared with CHOP plus etoposide, the economic model conducted scenario analyses which assumed that CHOEP has the same efficacy as CHOP. Conducting an ITC was deemed not feasible because of limitation in the available data.	Is the comparator, it's dose, and schedule a relevant current standard of care option in Canada? Are there other relevant comparator options in Canada (e.g., CHOEP)?	There is no reliable estimate of the comparative efficacy of brentuximab in combination with CHP to CHOEP. The CGP noted that the assumption that CHOP performs similarly to CHOEP is justified by available evidence[12] and clinical experience. However, the data suggest that the benefit of CHOEP was mostly seen in patients with ALK+ve sALCL whereas only a trend was noted in those with other subtypes including ALK-ve sALCL. CHOEP can thus be considered equivalent to CHOP in patients with ALK-ve sALCL, PTCL-NOS and AITL. For more details refer to section 1.2.4 of the CGP's interpretation. CGP agreed that overall brentuximab in combination with CHP would be the preferred first line treatment in PTCL.
Outcomes	**Appropriateness of primary and Secondary Outcomes**	Primary efficacy outcome: PFS per blinded institutional review facility (IRF). Secondary efficacy outcomes: PFS per IRF in the subset of patients with sALCL, complete remission (CR) rate per IRF following completion of study treatment, overall survival (OS), objective response rate (ORR) per IRF.	Do the trial endpoints limit the interpretation of the trial results with respect to the target population (e.g., do the trial outcomes typically guide treatment selection in clinical practice?)	The CGP agreed that PFS is an appropriate endpoint in the setting of PTCL. PFS is a well established clinically meaningful outcome and is used to guide treatment selection in clinical practice. Overall survival in this setting may be influenced by the heterogenous disease biology as well as the application of further therapies after progression.

Domain	Factor	Evidence from ECHELON-2 trial	Generalizability Question	CGP Assessment of Generalizability
Setting	**Countries participating in the trial**	The trial was conducted at 132 sites in 17 countries, including: Canada (3 sites, n=6, 1%) USA (30 sites; n=127, 28%) Japan (10%), South Korea (9%), Italy (8%), France (8%), Germany (6%), Spain (6%), Czech Republic (5%), UK (5%), Australia (3%), Denmark (3%), Israel (3%), Hungary (2%), Taiwan (2%), Poland (2%), Romania (0%)	If the trial was conducted outside of Canada, is there a known difference in effect based on ethnicity that might yield a different result in a Canadian setting? Also, if the demographics of the study countries differ from Canada, the average treatment effect in the trial might not be representative of a Canadian setting.	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.
	Supportive medications, procedures, or care	The use of one supportive medication, granulocyte-colony stimulating factor (G-CSF), was noted and permitted at the discretion of the treating physician based on institutional standards Primary prophylaxis with G-CSF was administered to 34% of BV+CHP-treated patients and 27% of CHOP-treated patients.	Does the use of supportive medication limit the interpretation of the trial results with respect to the target population?	Administration of G-CSF is considered standard of care in Canadian practice in selected patients. The trial results are generalizable to the Canadian patient population.

Abbreviations: AITL – angioimmunoblastic T-cell lymphoma; ALK – anaplastic lymphoma kinase; ATLL – adult T-cell leukemia or lymphoma; BV – brentuximab vedotin; CHOP – cyclophosphamide, doxorubicin, vincristine, prednisone; IV – intravenously; CHP – cyclophosphamide, doxorubicin, prednisone; CGP = pCODR clinical guidance panel; CI – confidence interval; EATL – enteropathy-associated T-cell lymphoma; ECOG – Eastern Cooperative Oncology Group; HTCL – hepatosplenic T-cell lymphoma; NOS – not otherwise specified; OS – overall survival; PFS – progression-free survival; po – by mouth; PS – performance status; PTCL – peripheral T-cell lymphoma; sALCL – systemic anaplastic large cell lymphoma

1.2.4 Interpretation

Burden of Illness and need

Systemic peripheral T-cell lymphoma (PTCL) is a broad category with several heterogeneous subtypes including PTCL- not otherwise specified (PTCL-NOS), systemic anaplastic large cell lymphoma (sALCL) and angioimmunoblastic T-cell lymphoma (AITL) that account for almost 70% of all cases with PTCL.[9,10] Despite their unique histologies, these subtypes have historically been managed similar to diffuse large B-cell lymphoma (DLBCL) using combination chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP)(3). However, unlike DLBCL, the outcome of patients with systemic PTCL [with the exception of anaplastic lymphoma kinase (ALK) positive sALCL] is suboptimal (5-year PFS 60% versus 35%).[9,10]

Several attempts have been made to improve upon CHOP induction by either the addition of other agents to CHOP or by utilizing novel induction regimens; disappointingly there had not been any signal of improved outcome.[13-22] There has been an analysis of prospective trials that showed superior outcome with a combination of CHOP + etoposide (CHOEP) in patients younger than 60 with a normal lactate dehydrogenase.[12] Even then, the benefit was mostly seen in patients with ALK+ve sALCL whereas only a trend was noted in those with other subtypes including ALK-ve sALCL. The CGP noted that in the absence of more robust direct evidence from a comparative randomized controlled trial, it seemed likely that CHOEP has similar efficacy to CHOP in patients with ALK-ve sALCL, PTCL-NOS and AITL. The CGP noted that toxicity seemed slightly higher (especially myelosuppression) with CHOEP compared with CHOP.[23,24] However, the CGP cautioned that there is insufficient evidence to determine the comparative effectiveness and safety of CHOP compared with CHOEP and therefore patient values and preferences, co-morbidities, individual toxicity profiles, and treatment availability (provincial reimbursement) should guide treatment selection.

Consolidative autologous stem cell transplantation (ASCT) after CHOP or CHOEP chemotherapy is commonly considered in order to optimize outcomes in this group of patients with poor outcomes.[23] However, in the absence of large prospective comparative randomized trials, an optimal management strategy remains uncertain and the application of consolidative ASCT varies depending on patients' age and comorbidities, but also individual centre's practices. The number of consolidative ASCTs received by patients in the ECHELON-2 trial (i.e., approximately 20% in each group) seems overall reflective of the Canadian landscape (while some centres commonly apply consolidative ASCT others do not).

Taken together, the current Canadian standard of care of patients with PTCL is either CHOP or CHEOP with or without autologous stem cell transplantation consolidation.

Effectiveness

ECHELON-2 trial is the first large, well-designed, prospective randomized trial to demonstrate overall meaningful improvements in outcomes (including PFS, OS, ORR, CR) of patients with CD30+ve PTCL treated with BV+CHP when compared to CHOP chemotherapy. Patient demographics noted median age was 58 years, 80% had advanced stage disease and most were Caucasian males. Most patients enrolled in the ECHELON-2 trial had sALCL (70%), followed by PTCL-NOS (16%) and AITL (12%) histology. Of the sALCL patients, 48% had ALK-ve sALCL and 21% with ALK+ve sALCL. It is important to note that this trial only included intermediate to high risk patients with ALK+ve sALCL as defined by the International prognostic index (IPI) score of 2 or higher.

In the group that received BV+CHP, this trial demonstrated better ORR [83% vs 72%, difference 11.1%, p= 0.0032)], improved CR rate (68% versus 56%, difference 11.9%, p= 0.0066), significantly improved overall median PFS (48.2 months versus 20.8 months) and an improved 75th-percentile OS (not reached vs 17.5 months). These results are a breakthrough in the management of PTCL that portends an overall poor prognosis.

In exploratory subgroup analyses, the BV+CHP group was associated with improved PFS in all the major subtypes except AITL (HR 1.4). Similarly, the BV+CHP group was associated with improved OS in all the major subtypes including AITL (HR 0.87). It should, however, be noted that the analysis was not powered to compare the efficacy of BV+CHP in different subtypes of PTCL. The only subgroup with a pre-specified alpha-controlled hypothesis was the sALCL subtype for the PFS outcome; hence the outcomes of exploratory analyses in the other subgroups are mostly hypothesis generating.

Considering 98% of patients enrolled had sALCL, PTCL-NOS and AITL histology, it is challenging to draw meaningful conclusions on the treatment effect of BV+CHP in patients with ATLL and EATL who accounted for the remaining 2% of the trial population. The CGP agreed that it is not possible to extrapolate the results seen in the ITT population to these subtypes, given the very small sample size and heterogeneous disease biology.

Even though the study was not powered to determine the efficacy among the CD30+ve PTCL-NOS and AITL subgroups, the trend in the exploratory analyses favored BV+CHP. The CGP noted that this trend is not surprising considering both PTCL-NOS and AITL are nodal PTCL similar to sALCL, and all patients had CD30-expressing tumours, which is the antigen targeted by BV.

In the ECHELON-2 trial, enrolment of patients with ALK-positive sALCL was limited to those with intermediate to high-risk disease noted by an IPI score of equal or greater than 2. As patients with ALK-positive sALCL with an IPI score of less than 2 were excluded from the trial, there is no data to support the generalizability of treatment benefit in this patient population. The four risk scores (low risk = 0 or 1; low intermediate risk = 2; high intermediate risk = 3; high risk = 4 or 5) of the IPI appear to predict the survival outcome of PTCL patients.[9-11] The IPI score is utilized in clinical practice in determining the prognosis for individual patients.

For the first time, a randomized prospective trial has noted a combination regimen with superior outcomes compared with CHOP. Based on these trial results, the CGP agreed that BV+CHP will be the preferred regimen for patients with (i) CD30+ve ALK-ve sALCL, (ii) CD30+ve ALK+ve sALCL with intermediate to high IPI score, and (iii) CD30+ve PTCL-NOS and AITL. For patients with ALK+ve sALCL with low IPI score and patients with ATLL and EATL, CHOP (+/- etoposide) will remain the treatment of choice.

The ECHELON-2 trial does not address the utility of upfront stem cell transplant in the first line setting, and no conclusions can be drawn about the outcomes of consolidative stem cell transplant after BV+CHP or CHOP from this trial.

Safety

The safety profile of BV+CHP is fortunately similar to CHOP. Serious adverse events were noted in 39% and 38% of patients in the BV group and CHOP group, respectively. Discontinuation rate and death due to adverse events were also similar. Even though there was slightly more incidence of gastrointestinal toxicities (nausea, vomiting, diarrhea) in the BV group, grade 3 or higher symptoms were similar. Many patients in BV group experienced fever and anemia but the rate of grade 3 or higher complication was comparable. It is important to note that the risk of neuropathy and neutropenia was similar in both groups. The safety profile was similar across all PTCL subgroups.

With respect to quality of life, BV+ CHP did not appear detrimental to quality of life with no clinically meaningful difference noted between the two groups.

1.3 Conclusions

The Clinical Guidance Panel (CGP) concluded that there is a net clinical benefit to the combination of CHP + BV compared with CHOP in the treatment of adults patients with ALK-ve sALCL and ALK+ve sALCL with IPI score of ≥ 2 based on one high-quality randomized controlled trial (ECHELON-2) that demonstrated a clinically and statistically significant benefit in OS and PFS for BV+CHP compared with CHOP with similar adverse event profiles between BV+CHP and CHOP.

The CGP also concluded that there may be a net clinical benefit to the combination of BV+CHP compared with CHOP in the treatment of adult patients with PTCL-NOS and AITL (both primary nodal PTCL like sALCL) based on a trend towards improved OS with similar adverse events profiles between CHP + BV and CHOP. All patients in the PTCL-NOS and AITL subgroups had CD30-expressing tumours, which is the antigen targeted by BV and conducting a randomized controlled trial is likely not feasible due to the infrequency of these subtypes with CD30-expressing tumours.

In making these conclusions, the CGP considered that this is the first large prospective randomized trial to show improved outcomes of PTCL patients with a novel combination regimen compared with CHOP.

Provincial Advisory Group's (PAG) Related Implementation Questions:

- The CGP agreed that patients currently treated with front-line chemotherapy should be addressed on a time-limited basis.
- With respect to PAG's queries about extending the use of BV+CHP to later lines of therapy or re-treatment with single agent BV after front-line BV+CHP, the CGP noted that currently there is insufficient evidence to use BV+CHP retreatment in patients who relapse following BV+CHP. There is also insufficient evidence regarding the efficacy of BV in combination with other agents in the relapsed/refractory setting. There is, however, evidence that BV as single agent is effective in patients with relapsed/ refractory CD30+ve PTCL. These patients did not receive BV with their prior lines. Pro B et al.[25] gave up to 16 cycles every 3 weeks and Horwitz S et al.[26] gave BV every 3 weeks until progression or toxicities. In the ECHELON-2 trial, BV+CHP was given for up to 8 cycles only. Thus, if a patient maintains at least a 6 months response following BV+CHP (i.e., they are not primary refractory) then BV as single agent may be utilized again, every three weeks, until further progression based on above evidence utilizing single agent BV in the relapse/ refractory setting.
- With respect to PAG seeking guidance on additional resources the CGP agreed 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.
- With respect to PAG seeking clarity on sequencing of treatments, the CGP noted that options for second line therapy are as follow (note that the order of preference will be at the discretion of the treating physician):
    - Multi-agent systemic therapy, e.g., GDP (gemcitabine, dexamethasone, platinum) or ICE (ifosfamide, carboplatin, etoposide) if the intent is stem cell transplantation (if patients did not receive upfront transplantation)
    - Brentuximab single agent in patients who received BV+CHP and experienced a durable response (greater than 6 months)
    - Histone deacetylase inhibitors like romidepsin
    - Pralatraxate
    - Single agent systemic chemotherapy e.g., gemcitabine
    - Clinical trial with novel agents.

2 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Lymphoma Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

2.1 Description of the Condition

T-cell lymphoma is a rare group of entities accounting for approximately 5 to 10% of all cases with Non-Hodgkin's lymphoma (NHL).[9] The 2016 edition of WHO classification listed different types of mature T-cell NHL (including natural killer (NK) cell neoplasms)[27]; these are broadly classified[28] as Cutaneous T-cell lymphomas [e,g., Mycosis Fungoides (MF), Sezary syndrome (SS), primary cutaneous CD30+, primary cutaneous gamma-delta]; Extra-nodal T-cell lymphomas [e.g., NK/T-cell nasal type (NK/TCL), Enteropathic associated T-cell lymphoma (EATL), Hepatosplenic, Sub-panniculitis like]; Nodal T-cell lymphomas [e.g., Peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), systemic Anaplastic large cell lymphoma (sALCL) which is ALK +ve or –ve, Angioimmunoblastic T-cell lymphoma (AITL)]; and Leukemic T-cell lymphomas [e.g., adult T-cell leukemia/lymphoma (ATLL), aggressive NK cell leukemia, T-cell prolymphocytic lymphoma (T-PLL), T-cell large granular cell leukemia (T-LGL)].

An International study that included patients from North America (including Canada), Europe and Asia showed that almost 57% of all T-cell lymphomas (TCL) were PTCL-NOS (26%), AITL (19%) and sALCL (12%) followed by rare entities like NK/TCL (10%), ATLL (10%) and EATL (5%).[9] There was, however, some geographical variation; in the North American sub-group PTCL-NOS, sALCL and AITL accounted for almost 75% (34%, 24% and 16%, respectively) of all cases with TCL. In a Canadian cohort from British Columbia, PTCL-NOS was found to be the most common TCL (59%) followed by sALCL (17%), EN/NK TCL (9%), AITL (5%) and EATL.[10]

2019 Canadian Cancer Statistics expected approximately 10,000 new cases of NHL per year and an age-standardized incidence rate of 24 cases per 100,000. Assuming ~ 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 PTCL-NOS, sALCL or AITL subtypes.[29]

2.2 Accepted Clinical Practice

Considering different types of TCL, management is often dependent on histologic subtype and its clinical behaviour. Indolently behaving TCL (eg. cutaneous TCL, T-LGL etco) is managed less aggressively with local therapies or mild immunosuppressive treatments. In contrast, the management of aggressive TCL warrants systemic chemotherapy and has often been extrapolated from the management of aggressive B-cell NHL.

In 1993, Fisher R et al compared four antracycline-containing combination regimens CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), m-BACOD (methotrexate, bleomycin, cyclophosphamide, vincristine, dexamethasone), ProMACE-CytaBOM (prednisone, methotrexate, doxorubicin, cyclophosphamide, etoposide, cytarabine, bleomycin) and MACOP-B (methotrexate, doxorubicin, cyclophosphamide, prednisone, bleomycin) in a randomized phase III trial including patients with large cell lymphomas (including TCL)[30]; this trial showed that the outcome of patients treated with each of these regimens was comparable albeit with lesser toxicity in the CHOP group. Hence, CHOP became widely utilized in treatment of aggressive T-cell lymphoma including PTCL-NOS, sALCL and AITL. Unfortunately, in contrast to diffuse large B-cell lymphomas [5-year overall survival (OS) ~ 60%], the outcome of patients with aggressive TCL has often been

poor (5-year OS ~ 35%) with the exception of patients with ALK+ sALCL (5-year OS ~ 65%).[9,10] The International T-cell lymphoma project showed that the 5-year OS of patients with PTCL, AITL, sALK+ve ALCL and ALK-ve sALCL was 32%, 32%, 70% and 49%, respectively.[9] In a Canadian series, 5-year OS for PTCL-NOS, AITL, ALK +ve sALCL and ALK-ve sALCL was 35%, 36%, 58% and 34%.[10] Both studies show that, except for ALK+ve sALCL, CHOP treated patients with aggressive TCL have a dismal outcome and an unmet clinical need.

Unlike other aggressive T-cell lymphomas, limited stage nasal NK/T-cell lymphomas are treated with combined chemo-radiation protocols. These protocols include platinum based induction regimens such as DeVIC (dexamethasone, etoposide, ifosphamide, carboplatin)[31], VIPD (etoposide, ifosphamide, cisplatin, dexamethasone)[32] and cisplatin followed by VIDL (etoposide, ifosphamide, dexamethasone, L-asparaginase).[33] SMILE regimen (dexamethasone, methotrexate, ifosphamide, L-asparaginase, etoposide) is widely used to treat advanced stage NK/T cell lymphoma.[34]

Several agents have been added to CHOP induction, including alemtuzumab[13-15], bortezomib[16], denileukin diftitox[17], bevacizumab[18] and everolimus[19] in single group studies, in an effort to improve the outcomes of these patients however there has been no signal of better results thus far.

The German High-grade Non-Hodgkin lymphoma (GHNHL) study group analyzed outcomes of patients with TCL treated in their prospective trials including CHOP with or without etoposide (CHOEP)[12]; they showed that the younger patients (< 60 years age) with normal lactate dehydrogenase (LDH) fared better with the addition of etoposide [3- year event-free survival (EFS) 75% vs 51%]. This benefit was significant for ALK+ve sALCL (3-year EFS 91% vs 57%) whereas only a trend was seen for the other TCL (3-year EFS of 61% vs 48%, p= 0.057). Based on these results, some centers offer CHOEP to patients < 60 years with a normal LDH. It should however be noted that this was not a head-to-head trial comparing CHOP with CHOEP.

A few prospective randomized studies compared CHOP to novel platinum containing induction combination regimens such as VIP-ABVD (etoposide, ifosphamide, cisplatin, doxorubicin, bleomycin, vinblastine, dacarbazine)[20], GEM-P (gemcitabine, cisplatin, methylprednisolone)[35] and GDP-T (gemcitabine, dexamethasone, cisplatin, thalidomide)[22] for the upfront treatment of aggressive TCL but the outcomes were similar compared to CHOP. Some randomised studies, including romidepsin + CHOP versus CHOP, are ongoing (clinical trials #NCT01796002).[36]

Many centers offer upfront consolidative stem cell transplant (SCT) to all patients (except to those with ALK+ sALCL) following induction front-line therapy. There is, however, a lack of good data to support the use of upfront autologous stem cell transplant (ASCT). A large retrospective review from Europe showed no benefit to upfront ASCT for patients who attained a complete (CR) or partial (PR) response following induction.[37]

Upon relapse, a variety of therapeutic approaches are pursued. For patients who are candidates for SCT but have not received SCT previously, multi-agent salvage chemotherapy including GDP and ICE is widely used. For patients who are not a candidate for aggressive therapy or have relapsed post-SCT, the choice is mainly single agent palliative therapies including Brentuximab (for patients who express CD30)[25,26], Histone deacetylase (HDAC) inhibitors (e.g.,[38] Romidepsin[39], belinostat[40,41]) and Pralatraxate.[42]

Brentuximab vedotin (BV) is effective in patients with CD30+ve TCL. A large phase II study of 58 patients with relapsed/refractory sALCL (72% were ALK-ve) treated with BV showed an overall response (ORR) of 86% and a CR of 66%; 5 year OS was 60%.[25] Similarly, a phase II study of CD30+ PTCL-NOS and AITL showed ORR of 41% (33% for PTCL-NOS, 54% for AITL)

and a CR rate of 24% (14% for PTCL-NOS and 38% for AITL).[26] The latter study showed no correlation between the level of CD30 expression and the outcome. Due to these outcomes in heavily treated patients with CD30+ sALCL, PTCL-NOS and AITL, BV has now been brought to the forefront in the management of untreated patients with CD30+ve TCL.[2]

ECHELON-2 study comparing CHOP versus CHP+BV (cyclophosphamide, doxorubicin, vincristine, brentuximab vedotin), in patients with CD30+ TCL (sALCL, PTCL-NOS and AITL accounted for 98% of patients) showed that the BV group had a median PFS of 48.2 months compared to only 20.4 months in the CHOP group.[2] This trial also showed survival benefit in the BV group (not reached versus 17.5 months). This landmark trial places CHP+BV as the frontline treatment for CD30+ sALCL, PTCL-NOS and AITL. This is supported by National Comprehensive Cancer Network (NCCN) guidelines (Category 1).[43]

Patients with systemic T-cell lymphoma (excluding EN NK/T-cell lymphoma and indolent TCL)		
Line of Therapy	CD30-ve aggressive TCL	CD30+ve PTCL-NOS, sALCL, AITL
1st-Line	CHOP or CHOEP then consolidative ASCT	CHP+BV (preferred) or CHOP/CHOEP +/- ASCT
Maintenance	None	None
2nd-Line	Salvage multiagent chemo (GDP/ICE) + SCT (if eligible) or palliative regimens	Salvage multiagent chemo (GDP/ICE) + SCT (if eligible) or palliative regimens

2.3 Evidence-Based Considerations for a Funding Population

2019 Canadian Cancer Statistics estimates 10,000 new cases of NHL per year of which approximately 700 cases (per year) will be of T-cell origin. 80% (560 patients) of these patients would have PTCL-NOS (~330 patients), sALCL (~ 95 patients) or AITL subtypes (~ 28 patients).[10]

All sALCL are CD30+[44] whereas 60% and 50% of PTCL-NOS and AITL, respectively, express CD30.[45] Based on this it is estimated that 198, 95, 14 patients with PTCL-NOS, sALCL and AITL, respectively, per year, will express CD30 (total 307 patients/year) thus making them eligible for CHP + BV. CD30 expression can be easily performed on tissue samples using immunohistochemistry. This test will be required to determine eligibility for CHP + BV.

2.4 Other Patient Populations in Whom the Drug May Be Used

CHP + BV will be only utilized for CD30+ PTCL-NOS, sALCL and AITL. BV as a single agent has however been widely used in relapsed/refractory Classical Hodgkin's lymphoma (CHL).[46,47] BV was recently evaluated for upfront treatment of untreated advanced stage CHL in combination with AVD (doxorubicin, vinblastine, dacarbazine)[48] but it is early to know if this will replace the current standard of ABVD (AVD + bleomycin). Single agent BV has also been evaluated in relapsed/refractory cutaneous CD30+ TCL[49-51].

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

The following patient advocacy group(s) provided input on Brentuximab-Vedotin (Adcetris) for the frontline treatment of patients with CD30-expressing Peripheral T Cell Lymphoma (PTCL), in combination with cyclophosphamide, doxorubicin, and prednisone (CHP) and their input is summarized below: Lymphoma Canada (LC).

LC submitted input based on data collected from one anonymous online survey conducted between September 16th, 2019 and October 20th, 2019 of PTCL patients. Survey links were sent via email to patients and caregivers registered on the LC database, as well as made available via LC Twitter and Facebook accounts, and international lymphoma organizations' own contacts. The survey had a combination of multiple choice, rating and open-ended questions. Skipping logic was built in so respondents were only asked questions that were relevant to them. LC stated that open-ended responses to the survey that reflected the sentiment of a majority were included verbatim to provide a deeper understanding of patient and caregiver perspectives. Overall, 13 PTCL patients provided input for this submission (the input did not note if patients were CD30+). Of these 13 respondents, 2 patients had experience with frontline treatment with Brentuximab-Vedotin (BV) in combination with CHP (BV+CHP). Eleven respondents provided information about their country, gender and age: five were from Canada, four were from the United States, one was from each the United Kingdom and Australia; 7 were males and 4 were females; their ages ranged from 30-69. The respondents' demographics are summarized in the table below (Table 1).

Table 1: Demographics of LC survey respondents.

	Patients **with** BV+CHP Experience (n=2)	Patients **without** BV+CHP Experience (n=11)
Country		
Canada	1	4
USA	1	3
UK	0	1
Australia	0	1
Skipped	0	2
Age Range		
<20	0	0
20-39	1	1
40-59	1	4
60-79	0	4
≥80	0	0
Did not answer	0	2
Gender		
Female	0	4
Male	2	5
Did not answer	0	2

From a patient's perspective the symptoms of PTCL that most commonly affected their quality of life 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, respondents all 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.

LC 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 and disease control.

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 advocacy groups.

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with PTCL

Of the 13 respondents to the LC survey, two were diagnosed with angioimmunoblastic T-cell lymphoma (AITL), four with anaplastic large-cell lymphoma (ALCL), two with from cutaneous T-cell lymphoma (CTCL), and five with peripheral T-cell lymphoma not otherwise specified (PTCL-NOS). Symptoms of PTCL that most commonly affected respondents' quality of life at diagnosis were fatigue or lack of energy (77%, n=10), fevers (62%, n=8), and enlarged lymph nodes (38%, n=5). Other symptoms affecting quality of life for ≥ 10% of respondents included unexplained weight loss, frequent infections, enlarged spleen, and shortness of breath.

When asked about which aspects of their lives had been negatively affected by cancer, 62% of respondents to LC's survey indicated that PTCL had a negative impact on their ability to work or study and on family obligations. Additional responses are listed below (Table 2).

Table 2. Effect of PTCL on day-to-day life of patients

Aspect of life Negatively impacted by PTCL	# of respondents	% of respondents
Ability to work	8	62%
Family obligations	8	62%
Physical activities	7	54%
Intimate relations	4	31%
Personal image	3	23%
Friendships	3	23%

Furthermore, the majority of respondents (77%) also reported that their quality of life was negatively affected by mental and emotional problems associated with their disease. Additional responses are listed below (Table 3).

Table 4: Effect of PTCL on current quality of life of patients

Symptom or problem related to PTCL	# of respondents	% of respondents
Anxiety/worry	8	62%
Problems concentrating	8	62%
Stress of diagnosis	7	54%
Difficulty sleeping	6	46%
None of these	3	23%
Memory loss	3	23%
Depression	3	23%
Loss of sexual desire	3	23%

When asked how living with PTCL had an impact on their day-to-day life and quality of life, three respondents provided the following responses:

"I had a stressful and demanding career and was not able to work after my diagnosis. I made the decision not to return to it after treatment. This had a big impact on myself and my family."

"Went off work due to pain and anxiety. Job then ended due to a layoff. Struggle to manage the anxiety behind it. Cannot do physically what I used to do as I get worn out easily."

"Little/no hockey during chemo. Significantly reduced professional activity and commensurate loss of income. Very high cost of unfunded Brentuximab"

3.1.2 Patients' Experiences with Current Therapy for PTCL

LC reported that two patients had experience with front-line treatment with BV+CHP, and 11 did not. Of the 11 respondents who had not received front-line treatment with BV-CHP, six (55%) were currently undergoing first-line treatment, three (27%) were undergoing third-line (or later) treatment, one (9%) was in remission following one line of therapy and one (9%) was in remission after three or more lines of therapy. Of the 10 respondents who provided information about their first-line therapy, six (60%) had received a cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) regimen, two (20%) had received a cyclophosphamide, hydroxydoxorubicin, vincristine, etoposide, prednisone (CHOEP) regimen, one (10%) had received a Hyper-cyclophosphamide, vincristine, doxorubicin, dexamethasone (CVAD) regimen, and one (10%) had received a topical steroid cream. Subsequent lines of therapy included CHOP, dexamethasone, high-dose cytarabine, cisplatin (DHAP), BV, PEG-asparaginase and autologous bone-marrow transplant.

When asked about the side effects of current treatment, respondents noted that nausea/vomiting and mouth sores were the most difficult side effects to tolerate. The most commonly reported side effects experienced during PTCL treatments from the eleven respondents to this question are listed below (Table 5).

Table 5: Side effects of current PTCL therapies

Side effect	% of respondents
Fatigue	82%
Nausea/vomiting	64%
Hair loss	64%
Mouth sores	36%
Neutropenia	27%
Infections	27%
Diarrhea	18%
Skin rashes/severe itching	18%
Infusion reaction	9%
Low platelets	9%
Bowel obstruction	9%
Breathing difficulties	9%
Viral reactivation (e.g. shingles)	9%
I did not experience any SEs	9%
Back pain	9%
Cough	9%

Patients were asked to rate on a scale of 1 (little impact) to 5 (significant impact) how their treatment experience affected their quality of life. Fatigue and activity levels were most significantly impacted by treatment, and more than half of respondents rated toleration of treatment and number of clinic visits as having a moderate to significant impact on their quality of life. Additional responses to the effect of PTCL therapies on quality of life from the eleven respondents to this question are listed below (Table 6).

Table 6: Effect of PTCL therapies on quality of life

Aspect of treatment	Significant impact (4-5)	Moderate impact (2-3)	Moderate to significant impact (2-5)
Treatment-related fatigue	7 (64%)	2 (18%)	9 (82%)
Activity level	5 (45%)	3 (27%)	8 (73%)
Toleration of treatment	1 (9%)	6 (55%)	7 (64%)
Number of clinic visits	2 (18%)	4 (36%)	6 (55%)
Infusion time	2 (18%)	2 (18%)	4 (36%)
Frequency of infections	1 (9%)	3 (27%)	4 (36%)
Number of infections	1 (9%)	3 (27%)	4 (36%)
Infusion reaction	1 (9%)	1 (9%)	2 (18%)

3.1.3 Impact of PTCL and Current Therapy on Caregivers

The patient inputs did not report the impact of PTCL on caregivers.

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for and Experiences To Date with BV+CHP

When patients in LC's survey were asked about the importance of having choice in deciding which drug to take based on known side effects and expected outcomes of treatment on a scale of 1 (Not Important as Long There is at Least One Treatment Choice) to 5 (Extremely Important to Have Choice of Treatment), all 13 (100%) respondents selected "5". Additionally, LC reports that all 13 (100%) of respondents felt there is currently a need for more treatment options for patients with PTCL.

Furthermore, LC reported that the majority of respondents were willing to tolerate significant side effects in new drug therapies. When asked if they would be willing to tolerate side effects with a new drug approved by Health Canada for the treatment of PTCL on a scale of 1 (Will Not Tolerate Any Side Effects) to 5 (Will Tolerate Significant Side Effects), nine respondents (69%) answered with '4' or '5'. When asked why they would be willing to tolerate these side effects, some of the patient comments included:
"I feel my life and family are worth trying whatever is available to best treat my cancer."
"Depending on the side effects that are possible, I think feeling poorly for a day or two but gaining time and quality of life in the longer run, is a fair trade."
"To survive."

When patients were asked to rate the importance of various outcomes for a new drug or treatment for PTCL, on a scale of 1 (Not important To Control) to 5 (Very Important To Control), LC reported that all outcomes were highly rated, with priority assigned to bringing about remission and living longer, which LC suggested that patients prioritize longer survival,

longer remission and disease control over other considerations. Additional responses to patient priorities for a new treatment are listed below (Table 7).

Table 7: Patient priorities for a new treatment

Treatment Outcome	Rating Average
Longer survival than current treatments	5
Longer remission than current treatments	5
Better quality of life than current treatments	4.8
Fewer side effects than current treatments	4.2

Furthermore, when asked about other aspects of PTCL that the respondents would consider as being important for a new drug to control, patients commented:

"I would be looking for a substantial and immediate response… to the drug"
"I would like to see a drug that cures, instead of one that simply manages the symptoms."
"All aspects are important for a healthy life, mentally and physically."

Two respondents to LC's survey had experience with BV+CHP as a frontline treatment for PTCL. Details of the two respondents are listed below (Table 8).

Table 8: PTCL patients with frontline BV+CHP treatment experience

Patient	Gender	Age	Location	Year of dx	Access to drug	Date started treatment
1	Male	40-49	Canada	2019	Paid out-of-pocket	2019
2	Male	20-29	USA	2016	Clinical trial	2016

When asked about which of their PTCL symptoms were managed by BV+CHP, one respondent was not experiencing any symptoms prior to treatment, and the second respondent reported that BV+CHP managed most of their disease symptoms, including enlarged lymph nodes, fever, shortness of breath, and anemia. LC reported that BV+CHP was well-tolerated by both respondents, and that the most difficult side effect to tolerate for both respondents was fatigue, which worsened throughout treatment. One respondent noted that an infusion reaction caused some distress, but that it only happened one time. Both respondents reported the following side effects experienced with BV+CHP treatment: fatigue, hair loss, mouth sores, and neutropenia. One respondent reported experiencing each of the following side effects: infections, diarrhea, infusion reaction, tingling or numbness (peripheral neuropathy), breathing difficulties, and/or constipation.
The two respondents were asked to rate how treatment impacted their quality of life on a scale of 1 (little negative impact) to 5 (significant negative impact). Both respondents reported that treatment was well tolerated overall. The following aspects of treatment impact on quality of life (and the average rating) were reported: Treatment-related fatigue (4), activity level (4), toleration of treatment (2.5), infusion time (2), number of clinic visits (1), number of infections (1), and frequency of infections (1).

When asked how BV+CHP had changed their health and well-being, the respondents provided the following responses:

"The treatments weren't as bad as I thought they'd be. I was able to keep working even though I was really tired all the time."

"Too early to tell. The outcome is what matters. If it improves chance of remission and long-term survival, then the therapy is well worth it."

Respondents were asked, based on their experience with the treatment regimen, if they would take this therapy again if their doctor thought it was the best choice. Both individuals responded "yes".

One respondent added the following comment:

"The scientific evidence is clear that Brentuximab significantly improves outcomes. So why is it not funded in Ontario? There is no good reason for Ontario to withhold funding. $100k is a lot of money for anybody, but for some it is impossible. Cut the red tape and fund it…"

3.3 Additional Information

None.

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

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 front-line treatment of patients with CD30-expressing peripheral T-cell lymphoma (PTCL) is combination chemotherapy with cyclophosphamide (C), doxorubicin (H), vincristine (O), and prednisone (P; CHOP) or CHOEP (CHOP plus etoposide), which are funded in all provinces. The ECHELON-2 trial compared brentuximab vedotin (BV) + CHP to CHOP, which is a relevant comparator, PAG is also seeking data compared to CHOEP.

4.2 Eligible Patient Population

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. PAG noted that the patient population is specific to those who are CD30 antigen positive.

PAG is seeking guidance on the use of BV in combination with other chemotherapy regimens.

If recommended for reimbursement, PAG noted that patients who have already initiated front-line chemotherapy treatment and who have not progressed would need to be addressed on a time-limited basis.

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 front-line treatment.

4.3 Implementation Factors

PAG noted that drug wastage is a significant barrier as only 50mg vials are available and patients may require up to four vials (180 mg = 1.8 mg/kg IV for 100kg patient) per treatment cycle. Furthermore, the drug has 24hr stability after reconstitution and vial sharing may be difficult with a very small number of eligible patients. 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. 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.

The recommended BV dosage for PTCL is 1.8 mg/kg up to a maximum of 180 mg in combination with CHP. PAG is seeking clarity on the treatment duration as the trial was up to 6 to 8 cycles, or until disease progression or unacceptable toxicity.

BV is an add-on therapy to currently available front-line combination chemotherapy. BV is already used for other indications and health care professionals are familiar with its preparation, administration and monitoring for adverse events.

4.4 Sequencing and Priority of Treatments

PAG noted that there are different therapies available for different histologic subtypes of T cell lymphoma. PAG is seeking clarity on the place in therapy of BV among the different treatments available and the possible sequencing of treatments:

- What treatment options would be available in the second-line setting upon progression with BV+CHP?
- PAG is seeking guidance on the appropriateness of re-treatment with single agent BV for sALCL or other CD30+ PTCL who receive front-line BV+CHP. If appropriate, what would be the appropriate time frame from completion of first-line treatment to relapse?

PAG also noted that romidepsin is funded in almost all provinces for relapsed/refractory PTCL. Pralatrexate recently received a positive conditional reimbursement recommendation for treatment of patients with relapsed or refractory PTCL, pralatrexate is under negotiations with the manufacturer.

4.5 Companion Diagnostic Testing

None.

4.6 Additional Information

None.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

The registered clinicians(s) provided input on Brentuximab-vedotin (BV) (Adcetris) for the frontline treatment of patients with CD30-expressing Peripheral T Cell Lymphoma (PTCL), in combination with cyclophosphamide, doxorubicin, and prednisone (CHP) and their input is summarized below: Two registered clinician input submissions were provided, representing a total of six clinicians. One joint input submission on behalf of five clinicians from British Columbia Cancer (BCC) as well as an individual input by a single hematologist from Cancer Care Ontario Hematology DAC.

Clinicians found that BV in combination with CHP (BV+CHP) provided benefit with regards to progression-free survival (PFS) and overall survival (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+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.

Please see below for a summary of specific input received from the registered clinician(s).

5.1 Current Treatment(s) for PTCL

The current provincial funding of treatments/funding algorithm for front-line treatment of patients with CD30-expressing PTCL is combination chemotherapy with cyclophosphamide (C), doxorubicin (H), vincristine (O), and prednisone (P) (CHOP), or CHOP plus etoposide (CHOEP), which are funded in all provinces.

The clinicians agreed that CHOP or CHOEP would be standard treatments for this patient population, and that this may be given with or without high dose chemotherapy and autologous stem cell transplant. They further stated that auto-transplant would be reasonable for patients in first remission. Clinicians also support that the comparator used in the ECHELON-2 study (CHOP) was an appropriate comparator for the Canadian treatment setting.

5.2 Eligible Patient Population

Overall, the clinicians agreed that the eligible patient population from the clinical trial would be reasonable for patients seen in clinical practice. They explained that therapeutic responses to front-line treatments are neither adequate not durable, and that PTCL has an overall inferior prognosis compared to aggressive B-cell lymphomas. They reported that approximately 25-30% of patients experience a long-term remission following induction therapy, and outcomes for relapsed PTCL are extremely poor, with median progression-free survival (PFS) being less than four months and median overall survival (OS) being approximately 6.5 months. The clinicians claimed that results are superior for ALK-positive anaplastic large cell lymphoma (ALCL), however patients with multiple international Prognostic Index factors have survival rates similar to other PTCL subtypes. The clinicians went on to state that most patients undergoing treatment for PTCL do not achieve remission or complete relapse, and therefore there is still a substantial unmet medical need for this aggressive and life-threatening disease. They noted that by incorporating a novel agent into front-line therapy, cure rates may be improved, and that BV+CHP is the first treatment in PTCL to show an OS benefit over CHOP.

The clinicians summarized that ECHELON-2 mandated that 75% of patients entering into the study have ALCL by European Union and Canadian regulatory commitment that this would represent a confirmatory trial for the original approval of BV in refractory or relapsed ACLC patients. They state that therefore, the large majority of patients entered into the study had ALK-negative or ALK-positive ALCL and appear to derive the greatest benefit from the addition of BV. The clinicians further mentioned that The Food and Drug Administration (FDA) has approved BV+CHP in all patients with CD30-expresing PTCL, however European Medicines Agency and Health Canada have not stipulated approval.

Implementation Questions: In clinical practice, is there evidence to extend the use of BV+CHP to (provided all other eligibility criteria are met):

a) The use of BV in combination with other chemotherapy regimens?

b) In later lines of therapies? For example, BV+CHP for second-line treatment following initial front-line chemotherapy.

The responses to the implementation questions are as follows:

a) The clinicians felt that, given the data available, they would limit BV to combination with CHP. They further stated that there is increasing toxicity with etoposide, so they would need more data before extending to other chemotherapies. Some clinicians noted that there is an ongoing phase 2 study evaluating the safety and efficacy of BV+CHEP in CD30 positive PTCL patients that may inform on usage with this chemotherapy backbone.
b) Some clinicians stated that there is currently no data for use in second line or later treatment, and therefore its use would be speculative. Furthermore, clinicians mentioned that BV+CHP is intended in primary therapy only. They did note that in select circumstances, it may be considered in later lane (ex. History of cutaneous ALCL treated with RADs with relapsed with systemic involvement).

5.3 Relevance to Clinical Practice

All the clinicians have experience using the treatment under review. The clinicians noted that brentuximab demonstrated improved OS and PFS at no additional toxicity and that this treatment seems to be tolerated by patients overall. They did however note that there is a high level of neuropathy.

Furthermore, the clinicians stated that BV+CHP would be used for front-line treatment of all patients with CD30-expressing PTCL, and that ALK-negative and ALK-positive ALCL patients would be the highest priority. The clinicians stated that the safety of BV-CHP was established in ECHELON-2, and while there was slightly more diarrhea, it was low grade. They summarized that unlike in an amendment to the trial ECHELON-1, growth factor support was not mandated in the ECHELON-2 trial, however it is recommended with FDA approval, and that it is a more intensive regimen and caution should be taken when administering to older patients. They noted that if a patient has a baseline peripheral neuropathy of Grade 2 or higher, BV should be avoided.

5.4 Sequencing and Priority of Treatments with BV in combination with CHP

The clinicians stated that BV+CHP would be used in front-line treatment settings for all eligible patients and would replace the current standard treatment of CHOP or CHOEP.

Implementation Questions: Please consider if there is evidence to support the optimal treatment sequencing with BV+CHP with available treatments for CD30+ PTCL:

a) What treatment options would be available in the second-line setting upon progression with BV+CHP?

b) The appropriateness of re-treatment with single agent BV for sALCL or other CD30+ PTCL who receive front-line BV+CHP. If appropriate, what would be the appropriate time frame from completion of first-line treatment to relapse?

The responses to the implementation questions are as follows:

a) Clinicians stated that upon progression, the standard care often recommended following first relapse for transplant-ineligible patients with chemosensitive disease is consolidation with high dose therapy and either autologous or allogeneic transplant, with the latter preferred for refractory disease and younger patients. They noted that many patients do not have chemo-sensitive disease and would be considered ineligible for transplant. They would recommend participation in a clinical trial if available for these patients. Clinicians stated that combination palliative chemotherapy, romidepsin or pralatrexate are approved by Health Canada, and could be used in this scenario, with some clinicians further specifying this use in older, less fit patients.
b) Clinicians stated that it may be reasonable to retreat with BV, particularly in refractory or relapsed ALCL patients. They mentioned that previous studies have shown a high response rate with retreatment, and as long as progressive disease is not demonstrated, then BV should be considered a viable option.

5.5 Companion Diagnostic Testing

Clinicians stated that CD30 expression testing is standard and routinely tested as part of the pathological assessment of PTCL, and that FDA approval dose not state percentage cut-off which is appropriate.

5.6 Additional Information

The clinicians from BCC summarized that in their views, BV+CHP represents the first major breakthrough in the treatment of PTCL and that given the PFS and OS benefit, it would be unethical to not fund this combination in Canada when guided by Health Canada approval guidelines. They further state that they are currently challenged in managing these patients as they do not have provincial access, and that it is urgent for BV+CHP to move through CADTH and reach provincial coverage.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the efficacy and safety of brentuximab vedotin (BV) in combination with cyclophosphamide (C), doxorubicin (H), and prednisone (P; CHP) compared to combination chemotherapy with cyclophosphamide, doxorubicin, vincristine (O), and prednisone (CHOP) or CHOP-like regimens 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.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the CGP and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below. 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 pCODR Methods Team are provided in Appendix A.

Table 6.1. Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
• Published or unpublished RCTs	• Patients with CD30-expressing peripheral T-cell lymphoma (PTCL) one of the following histologies: o Alk+ sALCL (with IPI score ≥2) o ALK- sALCL o PTCL NOS o Angioimmunoblastic TCL • Treatment naïve (no previous treatment for CD30-expressing PTCL • Subtypes of PTCL	Brentuximab vedotin (BV) in combination with CHP BV dosage for PTCL is 1.8mg/kg up to a max of 180mg; IV infusion over 30 minutes for 3w for 6-8 cycles, or until disease progression or unacceptable toxicity	• Combination chemotherapy with CHOP • Combination chemotherapy with CHOEP	• **OS** • PFS • PFS for pts with sALCL • Toxicity (type incidence, severity) • CR • OS • ORR • Laboratory abnormalities • MRU • QOL
Abbreviations: ATA – antitherapeutic antibodies; BV – brentuximab vedotin; C – cyclophosphamide; CR – complete remission; E – etoposide; H – doxorubicin; IV – intravenous; MRU – medical resource utilization; NOS – not otherwise specified; O – vincristine; ORR – objective response rate; OS – overall survival; P – prednisone; PFS – progression-free survival; PTCL – peripheral T-cell lymphoma; pts – patients; QOL – quality of life; RCTs – randomized controlled trials; sALCL – systemic anaplastic large cell lymphoma; TCL – T-cell lymphoma; w - weeks				

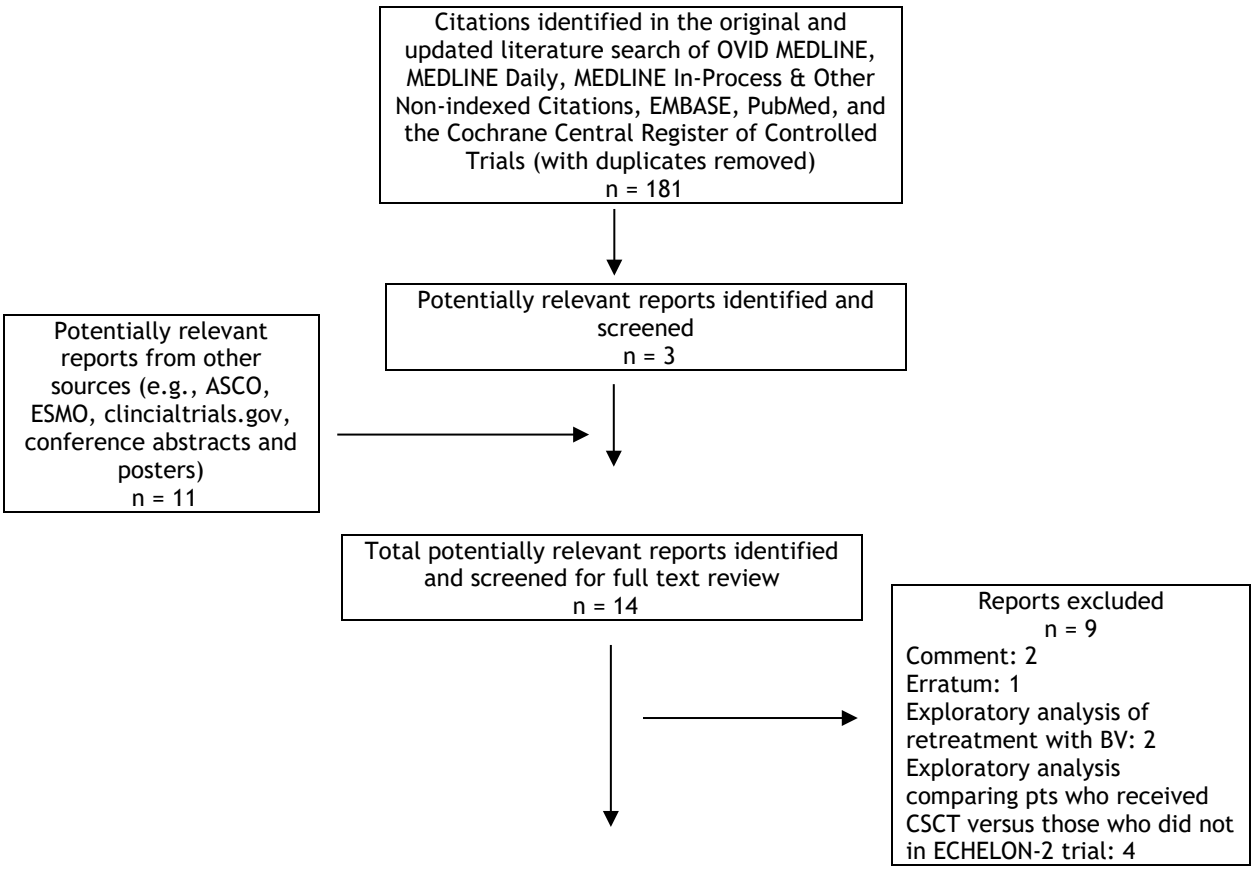
** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

6.3 Results

6.3.1 Literature Search Results

Of the 3 potentially relevant reports identified, one study was included in the pCODR systematic review[2] and 2 studies were excluded because they were subgroup analyses of response to brentuximab + CHP by CD30 expression in the ECHELON-2 trial[52,53].

Figure 6.1. QUOROM Flow Diagram for Inclusion and Exclusion of studies



Abbreviations: BV – brentuximab vedotin; CSCT – consolidative stem cell tranplant; pts - patients

Note: Additional data related to studies ECHELON-2 were also obtained through requests to the Submitter by pCODR.

6.3.2 Summary of Included Studies

One randomized controlled trial, ECHELON-2[2], was identified that met the eligibility criteria and is included in this review. Characteristics of the trial are summarized in Table 6.2 and specific aspects of trial quality are summarized in Table 6.3.

6.3.3 Detailed Trial Characteristics

Table 6.2 Summary of Key Characteristics of the ECHELON-2 trial.

Trial Design	Eligibility Criteria	Intervention	Comparator	Trial Outcomes
ECHELON-2 Phase 3, double-blind, double-dummy, placebo-controlled RCT (1:1)[2] Patient Enrolment: January 24, 2013 to November 7, 2016 Primary analysis data cut-off date (actual primary completion date): August 15, 2018 Estimated study completion date: August 15, 2020[3] N randomized=452 n treated=449 Multicenter: 132 sites in 17 countries including Canada[2] Randomization stratified by: • IPI score (0–1 vs 2–3 vs 4–5) • Alk-positive sALCL versus all other histological subtypes Funded by Seattle Genetics, Inc., Millennium Pharmaceuticals Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Ltd, and the	<u>Key Inclusion Criteria:</u>[2] • Pts ≥18 yrs with newly diagnosed previously untreated CD30-positive[a] PTCL[b] • Eligible histologies included ALK+ sALCL with IPI score ≥2, ALK- sALCL, PTCL NOS, AITL, ATLL, EATL, hepatosplenic TCL • ECOG PS ≤2 • Total bilirubin ≤1.5 times ULN (≤3 times ULN for subjects with Gilbert's disease or documented hepatic involvement with lymphoma, and serum creatinine ≤2 times ULN • FDG-avid disease by PET and measurable disease of at least 1.5cm by CT <u>Key Exclusion Criteria:</u>[2] • Previous history of another primary invasive cancer or hematological malignancy • Current diagnosis of any of the following: 1) primary cutaneous CD30-positive T-cell lymphoproliferative disorders and lymphomas. Cutaneous ALCL with extracutaneous tumour spread beyond locoregional lymph nodes were eligible	21-day cycles[c] of: CHP (cyclophosphamide 750mg/m^2 and doxorubicin 50mg/m^2 IV on day 1 of each cycle and prednisone 100mg once daily orally on days 1-5 of each cycle + Brentuximab vedotin 1.8mg/kg IV on day 1 of each cycle + Placebo form of vincristine	21-day cycles[c] of: CHOP (cyclophosphamide 750mg/m^2 and doxorubicin 50mg/m^2 IV on day 1 of each cycle and prednisone 100mg once daily orally on days 1-5 of each cycle + Vincristine 1.4mg/m^2 (max 2.0mg/m^2) IV on day 1 of each cycle + Placebo form of brentuximab vedotin	<u>Primary:</u> • PFS per independent review facility (IRF) <u>Secondary:</u> • PFS per IRF in pts with sALCL • Complete remission rate per IRF at end of treatment • OS • ORR • AE[6] Laboratory abnormality

Trial Design	Eligibility Criteria	Intervention	Comparator	Trial Outcomes
NIH National Cancer Institute Cancer Center[2]	2) MF, including transformed MF • History of progressive multifocal leukoencephalopathy Cerebral/meningeal disease related to underlying malignancy			

Table 6.3 Select quality characteristics of the included ECHELON-2 trial.

Study	ECHELON-2
Treatment versus Comparator	B+CHP versus CHOP
Primary outcomes	PFS
Required sample size	450
Sample size	452
Randomization method	Stratified[a] Centrally, using interactive web response system that assigned a unique patient randomization number and did not specify the actual treatment assignment[2]
Allocation concealment	Yes
Blinding	DB[b]
ITT Analysis	Yes
Final analysis	Yes[c]
Early termination	No
Ethics Approval	Yes

Notes: [a] – randomization was stratified by histological subtype according to local pathology assessment (ALK+ sALCL versus all other histologies) and baseline IPI score (0-1 versus 2-3 versus 4-5)
[b] – Brentuximab vedotin and vincristine were dispensed in a double-blind, double-dummy manner. The pharmacist at each study site, investigators, patients, BICR, and the sponsor were masked to treatment assignment.
[c] - The results from the data cut (August 15, 2018) are considered the final analyses of PFS (primary endpoint), OS (key secondary endpoint) and all other key secondary endpoints (CR, ORR). Upon request, the sponsor noted that as the primary and all alpha-controlled key secondary endpoints were met, there are no further multiplicity-adjusted analyses planned. Future analyses may be conducted and will be descriptive only.[54]
Abbreviations: B – brentuximab; BICR – blinded independent central review; C – cyclophosphamide; DB – double-blind; H – doxorubicin; O – vincristine; P – prednisone; PFS – progression-free survival; sALCL – systemic anaplastic large cell lymphoma

a) Trial

ECHELON-2 is a phase 3, international, multi-centered, double-blind, double-dummy, active-controlled randomized controlled trial. The aim of the study was to compare the efficacy and safety of brentuximab vedotin (BV) and cyclophosphamide, doxorubicin, and prednisone (CHP) versus cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) for the treatment of CD30-positive peripheral T-cell lymphomas (PTCL). There were 132 sites in 17 countries, including Australia, Canada, Czech Republic, Denmark, France, Germany, Hungary, Israel, Italy, Japan, Poland, Republic of Korea, Romania, Spain, Taiwan, United Kingdom,

and United States of America that participated in the trial.[2] Four Canadian sites took part in the trial; 1 in Montreal, 1 in Toronto, 1 in Edmonton and 1 in Vancouver.[3] The trial sponsor, Seattle Genetics Inc., was involved in the design of the trial, collection, interpretation, and analysis of the data, and provided funding assistance with medical writing.[2] All authors had access to the study data and contributed to manuscript development.[2] Key eligibility criteria are outlined below and in Table 6.2.

Eligibility Criteria

Patients enrolled in the ECHELON-2 trial met the following inclusion criteria[6]:

- 18 years or older
- Newly diagnosed, CD30-positive mature T-cell lymphomas. CD30 positivity was defined when the following criteria were met: (i) CD30 detected in ≥10% of neoplastic cells (in cases where enumeration of neoplastic cells is not possible, total lymphocytes may be used), (ii) CD30 staining at any intensity above background, and (iii) membranous, cytoplasmic, and/or golgi pattern of expression of the CD30 antigen.[55]
- Fluorodeoxyglucose (FDG)-avid disease by PET and measurable disease of at least 1.5cm by CT
- Eastern Cooperative Oncology Group (ECOG) performance status ≤2

Exclusion Criteria

- History of another primary invasive malignancy that has not been in remission for at least 3 years
- Current diagnosis of primary cutaneous CD30-positive T-cell lymphoproliferative disorders and lymphomas or mycosis fungoides
- History of progressive multifocal leukoencephalopathy (PML)
- Cerebral/meningeal disease related to the underlying malignancy

Outcomes

The primary outcome of interest was progression-free survival by independent review facility measured up to 60 months[6]. PFS was defined as the time from the date of randomization to the date of the first event of relapse or progressive disease (PD), death due to any cause, or receipt of subsequent chemotherapy for residual or PD at the investigator's discretion.[2] In the absence of PD, radiotherapy to consolidate initial response or chemotherapy for mobilizing haemopoietic stem cells or consolidative stem cell transplantation were not considered disease progression events.[2] Secondary outcomes included PFS by institutional review facility (IRF) in patients with systemic anaplastic large cell lymphoma (sALCL) (up to 60 months), and complete remission rate (CRR) by IRF at end of treatment (EOT).[6] The number of patients who achieved complete remission (CR) at EOT was also measured. Overall survival (OS) was measured until death or study closure, up to 7 years post-treatment. Objective response rate (ORR) by IRF at EOT (time frame up to 8.34 months) and the number of patients who achieved CR or partial response (PR) at EOT was measured. Incidence of adverse events (AEs) and incidence of laboratory abnormalities were both measured up to 8.28 months. The

number of patients who experienced a Grade 3 or higher laboratory toxicity was also measured.[6]

Randomization, Blinding, Sample Size, and Statistical Analyses

Information on randomization, required sample size, statistical assumptions, and other quality indicators are outlined in Table 6.3.

Patients were randomized in a 1:1 ratio to the BV+CHP and CHOP treatment groups using a double-blind, double-dummy, placebo-controlled, centralized, and stratified method. A unique patient randomization number was assigned using an interactive web-response system, which did not specify the actual treatment assignment.[2] Patients were stratified according to histological subtype (ALK-positive sALCL versus all other histologies) and baseline IPI score (0-1, versus 2-3, versus 4-5). Randomized patients received either BV+CHP or CHOP administered every 21 days for six to eight cycles, as determined by the investigator at registration. The patients, investigators, independent central review committee, and sponsors were all masked to treatment assignment. Furthermore, the pharmacist preparing the BV, vincristine, and their placebo replacements was also masked at each site.[2]

Randomization of approximately 450 patients (225 patients per treatment group) over 42 months was planned to achieve (with 95% probability) 238 events in approximately 60 months, assuming 42 months of patient accrual and given an anticipated drop-out rate of 5% and 18 months of PFS follow-up after randomization of the last patient.[2] This sample size was planned in order to target 75% (±5%) of patients with a diagnosis of sALCL according to central pathology assessment to ensure the secondary outcome of PFS in sALCL could be appropriately assessed. The trial was powered on the assumption of median PFS of 23.9 months for the BV+CHP group and 16.5 months for the CHOP group. An estimated 238 PFS events would provide approximately 80% power to detect a hazard ratio (HR) for disease progression or death due to any cause of 0.6895 using the log-rank test and an overall one-sided alpha of 0.025 (two-sided alpha level of 0.05).[2] A total of four protocol amendments were made[56]. In general most amendments were administrative in nature to enhance clarity or safety precautions.[55] Two of the amendments related to planned sample size and timing of the analysis of the primary outcome. It is not expected that any of the protocol amendments had any significant impact on the observed study outcomes.

A stratified log-rank test (by randomization stratification factors) was used in order to compare differences in PFS between the treatment groups for the primary efficacy analysis. The estimation of HR was based on the stratified Cox regression model. The Kaplan Meier method was used to summarize PFS and similar methods were used for the key secondary efficacy endpoints. The reverse Kaplan-Meier method was used to calculate the PFS and OS median follow-up. The proportion of patients achieving an objective response and CR rate between the two treatment groups was tested using the Cochran-Mantel-Haenzel test, which was stratified by the randomization stratification factors.[2]

Details on methods to control for multiple comparisons or multiplicity are outlined in the statistical analysis plan.[57] The overall one-sided alpha level for the primary endpoint is 0.025. Additionally, the fixed sequence testing procedure outlined below ensures control of the family-wise error rate at a one-sided alpha level of 0.025 (Westfall 2001).

Formal statistical tests will be performed for PFS per IRF, and the key secondary endpoints of PFS per IRF for patients with centrally confirmed sALCL, CR rate per IRF and OS. If the test for the primary analysis of PFS per IRF is statistically significant in favor of the experimental group at a one-sided alpha level of 0.025, formal statistical tests will be performed for the key secondary endpoints of PFS per IRF for patients with centrally confirmed sALCL, CR per IRF and OS at an overall one-sided alpha level of 0.025. A fixed sequence testing procedure, where testing is carried out sequentially at an unadjusted alpha level as long as all preceding null hypotheses are rejected, will be used to ensure type I error control for key secondary endpoints. The testing order will be: 1) PFS per IRF for patients with centrally confirmed sALCL; 2) CR per IRF; 3) OS; and 4) ORR per IRF. If the test for PFS per IRF is not statistically significant, the p-value of the tests for PFS per IRF for patients with centrally confirmed sALCL, CR per IRF, OS, and ORR per IRF will still be calculated, but will be considered descriptive. [57]

Based on this pre-specified testing approach all of the primary and key secondary endpoints identified above were statistically significant.

Sensitivity analyses of PFS per IRF were pre-planned and mainly included changes regarding censoring rules. The sensitivity analyses were not multiplicity-adjusted, and no p-values were calculated[57]f

An Independent Data Monitoring Committee monitored safety, assessed the results of an interim analysis for futility, and conducted a review for overall survival as well as serious adverse events. Unless otherwise specified, all efficacy evaluations included the intention-to-treat (ITT) population. Safety was analysed in all patients who received any amount of BV or any component of CHOP.[2]

b) Population

Patients were enrolled in the ECHELON-2 trial between January 24, 2013 and November 7, 2016[6]. During that time, 601 patients were assessed for eligibility and 452 patients across 17 countries (including 6 patients from Canada[3]) were randomly assigned to the BV+CHP group (n=226) or the CHOP group (n=226) (Table 6.7). Overall, the baseline characteristics were well balanced between the two treatment groups (Table 6.4 and 6.5).[6] The median age was 58 years, with 69.2% of patients falling in the 19-64 age range.[6] The majority of patients were male (62.8%), and most patients were white (62.2%) or of Asian decent (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%).[2] Most patients had an ECOG performance status of 0 (39.2%) or 1 (38.9%), with 21.7% having a performance status of 2. Just over half of all randomized patients had Stage IV disease at diagnosis (53.1%) and 78.8% had IPI scores ≥2.[2]

c) Interventions

Patients enrolled in the ECHELON-2 trial received 21-day cycles of either BV+CHP or CHOP. After randomization, all patients were treated with the CHP components of the CHOP regimen, which included cyclophosphamide 750mg/m^2 and doxorubicin 50mg/m^2 intravenously on day 1 of each cycle and prednisone 100mg once daily orally on days 1-5 of each cycle. The number of cycles (6 or 8) 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+CHP group received 1.8mg/kg of BV intravenously on day 1 of each cycle and patients in the CHOP group received vincristine 1.4mg/m^2 (maximum 2.0mg) intravenously on day 1 of each cycle) after administration of CHP.[2] Cross-over was not permitted at any time during the study.[3] If a patient relapsed during or after treatment, unblinding could be requested and off study therapy could be subsequently administered.[3] All patients received treatment until 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.

In cases of adverse events, dose interruption (or reduction) of blinded study treatment, cyclophosphamide or doxorubicin was permitted when necessary.[2] Dose modifications were permitted for study treatment-associated neuropathy. Dose modifications for the 223 patients in the BV+CHP group and the 226 patients in the CHOP group for the safety analysis set included: 1) dose delay of BV due to AEs for 59 patients (26%) and dose reduction of BV for 21 patients (9%). A total of 88/1329 doses (7%) of BV were reduced due to AEs[4]. On the CHOP group, doses of vincristine were delayed due to AEs for 28 patients (12%) and reduced to due AEs for 24 patients (11%). A total of 41/1307 doses (3%) of vincristine were reduced due to AEs [4].

The median follow-up was 36.2 months (95%CI 35.9-41.8) and most patients completed the treatment as intended, with 198 (89%) in the BV+CHP group and 184 (81%) in the CHOP group receiving 6 or more treatment cycles. The proportion of patients receiving more than 6 cycles was 19% in both treatment groups (n=42 in the BC+CHP group and n=44 in the CHOP group). The median relative dose intensity was 99.2% (IQR 93.6-100.0) for BV in the BV+CHP group and 99.1% (IQR 95.9-102.3) for vincristine in the CHOP group.[2]

Consolidative therapies, including stem cell transplantation (with the intent prespecified before the first cycle of chemotherapy) and/or radiotherapy after treatment were permitted at the investigator's discretion[2] after at least six cycles of treatment.[5] A total of 39% (89/226) of patients randomized to the BV+CHP group and 36% (81/226) of patients in the CHOP group were prespecified by the investigator at baseline to receive consolidative stem cell transplantation.[2] Data on the number (and percentage) of patients receiving consolidative therapies are presented in Table 6.6.

The use of one concomitant medication, granulocyte-colony stimulating factor (G-CSF), was noted and permitted at the discretion of the treating physician based on institutional standards.[2] In May 2015, the IDMC recommended that Seattle Genetics remind investigators to administer G-CSF in accordance with American Society of Clinical Oncology (ASCO) or European Society of Medical Oncology (ESMO) guidelines.[2] Primary prophylaxis was defined as the administration of G-CSF during Cycle 1, on Day 1 through Day 8. Primary prophylaxis with G-CSF was administered to 34% of BV+CHP-treated patients and 27% of CHOP-treated patients.[5]

Table 6.4 Baseline characteristics of patients included in the ECHELON-2 trial.

	A+CHP group (n=226)	CHOP group (n=226)
Sex		
Men	133 (59%)	151 (67%)
Women	93 (41%)	75 (33%)
Median age, years (IQR)	58·0 (45–67)	58·0 (44–67)
Race		
Asian	45 (20%)	54 (24%)
Black or African American	12 (5%)	6 (3%)
White	139 (62%)	142 (63%)
Native Hawaiian or other Pacific Islander	1 (0%)	0
Other or unknown	29 (13%)	24 (11%)
ECOG performance†		
0	84 (37%)	93 (41%)
1	90 (40%)	86 (38%)
2	51 (23%)	47 (21%)
Diagnosis‡		
sALCL	162 (72%)	154 (68%)
ALK positive	49 (22%)	49 (22%)
ALK negative	113 (50%)	105 (46%)
PTCL-NOS	29 (13%)	43 (19%)
AITL	30 (13%)	24 (11%)
ATLL	4 (2%)	3 (1%)
EATL	1 (0%)	2 (1%)
Disease stage at diagnosis§		
1	12 (5%)	9 (4%)
2	30 (13%)	37 (16%)
3	57 (25%)	67 (30%)
4	127 (56%)	113 (50%)
Baseline IPI score¶		
0	8 (4%)	16 (7%)
1	45 (20%)	32 (14%)
2	74 (33%)	78 (35%)
3	66 (29%)	66 (29%)
4	29 (13%)	25 (11%)
5	4 (2%)	9 (4%)

Data are n (%), unless stated otherwise. Data shown are for the intention-to-treat population. A+CHP=brentuximab vedotin, cyclophosphamide, doxorubicin, and prednisone. AITL=angioimmunoblastic T-cell lymphoma. ALK=anaplastic lymphoma kinase. ATLL=adult T-cell leukaemia or lymphoma. CHOP=cyclophosphamide, doxorubicin, vincristine, and prednisone. EATL=enteropathy-associated T-cell lymphoma. ECOG=Eastern Cooperative Oncology Group. IPI=international prognostic index. PTCL-NOS=peripheral T-cell lymphoma not otherwise specified. sALCL=systemic anaplastic large cell lymphoma. *A full description of baseline characteristics can be found in the appendix. †Values for ECOG performance status range from 0 to 5, with higher scores indicating greater disability. ‡Diagnosis per local assessment. §The Ann Arbor staging system ranges from 1 to 4, with higher stages indicating more widespread disease. ¶The IPI score is calculated based on a patient's disease characteristics and represents increasing degrees of risk.

Source: Reprinted from The Lancet, Vol 393 number 12, Horwitz S, O'Connor OA, Pro B, et al., Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial., Pages No.229-240 and supplementary appendix, Copyright (2019), with permission from Elsevier[2]

Table 6.5 Additional Baseline characteristics of patients included in the ECHELON-2 trial.

Characteristic	A+CHP (N=226)	CHOP (N=226)
Time from diagnosis to first dose of study treatment (months) n		
	222	224
Mean (standard deviation)	1·1 (1·5)	1·1 (0·9)
Median	0·8	0·9
Min, Max	0, 19	0, 10
Initial diagnosis of cutaneous ALCL (for subjects with sALCL)	13 (6%)	4 (2%)
Time from cutaneous ALCL diagnosis to sALCL diagnosis (months)		
n	11	4
Mean (standard deviation)	16·0 (20·6)	9·8 (12·8)
Median	4·8	4·7
Min, Max	1, 69	1, 29
Serum LDH per local laboratory,		
≤1 × upper limit of normal	113 (50%)	97 (43%)
>1 × upper limit of normal	113 (50%)	129 (57%)
Extranodal disease involvement		
≤1 site	142 (63%)	146 (65%)
>1 site	84 (37%)	80 (35%)
HTLV-1 status		
Positive	5 (2%)	4 (2%)
Negative	216 (96%)	219 (97%)
Intended number of cycles		
6	185 (82%)	182 (81%)
8	41 (18%)	44 (19%)
Intention of stem cell transplant following completion of study regimen		
Yes	89 (39%)	81 (36%)
No	136 (60%)	144 (64%)
Baseline bone marrow biopsy-lymphoma involvement		
Yes	30 (13%)	34 (15%)
No	196 (87%)	192 (85%)
Percent CD30 positive cells, per local assessment n		
	224	226
Mean (standard deviation)	76·5 (32·7)	77·0 (30·7)
Median	90·5	90·0
Min, Max	10, 100	10, 100
Percent CD30 positive cells, per central review n		
	222	220
Mean (standard deviation)	81·1 (28·4)	77·6 (30·6)
Median	95·0	90·0
Min, Max	0, 100	0, 100

Data are n (%), unless stated otherwise. Data shown are for the intention-to-treat population. Percentages may not total 100 because of rounding. A+CHP=brentuximab vedotin, cyclophosphamide, doxorubicin, and

Source:

Reprinted from The Lancet, Vol 393 number 12, Horwitz S, O'Connor OA, Pro B, et al., Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial., Pages No.229-240 and supplementary appendix, Copyright (2019), with permission from Elsevier[2]

Table 6.6 Consolidative therapies received by patients in the ECHELON-2 trial.

	BV+CHP	CHOP
Patients who received consolidative treatment, n (%)[a]	61 (27.0)	44 (19.5)
Consolidative radiotherapy	14 (6.2)	6 (2.7)
Consolidative stem cell transplant	50 (22.1)	39 (17.3)
Autologous	49 (21.7)	39 (17.3)
Allogeneic	1 (0.4)	0 (0)

Notes: [a] – Patients may have received more than one type of therapy

Abbreviations: BV – brentuximab vedotin; C – cyclophosphamide; H – doxorubicin; n – number; O – vincristine; P - prednisone

Source: Reprinted from The Lancet, Vol 393 number 12, Horwitz S, O'Connor OA, Pro B, et al., Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial., Pages No.229-240 and supplementary appendix, Copyright (2019), with permission from Elsevier[2]

a) Patient Disposition

The disposition of the patients through the ECHELON-2 trial is summarized in Table 6.7. Of the 601 patients screened for eligibility in the trial, 452 were randomly assigned to BV+CHP versus CHOP[2]. Overall, 449 patients (99.3%) received the allocated treatment.[5] Three patients in the BV+CHP group were randomized but did not receive the study treatment[2] (one patient withdrew consent prior to treatment, one patient died prior to treatment, and one was found to be ineligible after randomization and was withdrawn from the study).[3] Of the patients receiving the allocated treatment, 82% of BV+CHP and 81% of CHOP patients were predetermined at baseline by the investigator to receive 6 cycles of treatment (compared to 8 cycles).[2] The median number of treatment cycles per patient was 6.0 (min: 1, max: 8)) for BV+CHP and 6.0 (min: 1, max: 8) for the CHOP group. The median duration of treatment was 18.1 weeks (min: 3; max: 34) and 18 weeks (min: 3, max: 31) in the BV+CHP and CHOP groups, respectively.[2]

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+CHP group and 139 (62%) in the CHOP group.[5] A total of 370 (82%) patients have completed treatment; 192 (85%) patients in the BV+CHP group and 178 (79%) in the CHOP group. Of the 449 patients who received the allocated treatment, 79 (17.6%) patients have discontinued treatment. Thirty-three patients (7.3%) discontinued due to progressive disease; 7 (3%) in the BV+CHP group and 26 (12%) in the CHOP group. There has been an equal number of treatment discontinuations due to adverse events, with 15 (7%) patients in each group stopping treatment for this reason.[5]

A total of 65 patients (29%) in the BV+CHP group and 96 patients (42%) in the CHOP group received subsequent anticancer therapy.[2] Patients may have received more than one type of therapy. Of those patients that received subsequent therapy, 59 patients (26%) in the BV+CHP group and 94 patients (42%) in the CHOP group received systemic therapy for residual or progressive disease and among those patients 23 (10%) in the BV+CHP group and 49 (22%) in the CHOP group received BV-containing regimens. Ten patients (4%) in the BV+CHP group and 8 (4%) in the

CHOP group received palliative radiation. Seven patients (3%) in the BV+CHP and 3 (1%) in the CHOP group received systemic therapy for other malignancies.

The CADTH Methods Team reviewed important protocol violations and noted that they were comparable between groups and not expected to impact the study results.[4]

Table 6.7 Patient disposition in the ECHELON-2 trial

Patient Disposition, n (%)	ECHELON-2	
Treatment Groups	**BV+CHP**	**CHOP**
Patients screened	601	
Patients randomized	226 (100)	226 (100)
Received allocated treatment	223 (99)	226 (100)
Did not receive allocated treatment	3 (1.3)[a]	0 (0)
Completed treatment	192 (85.0)	178 (78.8)
Patients remaining in long term follow up (ongoing in study)	157 (69.5)	139 (61.5)
Patients excluded from long term follow up	69[a] (30.5)	87 (38.5)
Withdrew	16 (7.1)	10 (4.4)
Deaths	51 (22.6)	73 (32.3)
Other reasons	2[b] (0.9)	0 (0)
Lost to follow up	0 (0)	4 (1.8)
Patients discontinuing randomized treatment	31 (13.7)	48 (21.2)
Progressive disease	7 (3.1)	26 (11.5)
Adverse events	15 (6.6)	15 (6.6)
Investigator decision	5 (2.2)	2 (0.9)
Other	4 (1.8)	5 (2.2)

Notes: [a] – Includes three patient who were randomly assigned to the BV group but did not receive study treatment (1 patient withdrew consent prior to treatment, 1 patient died prior to treatment, and 1 patient was found to be ineligible after randomization and was withdrawn from the study. [3]

[b] – Other reasons for study discontinuation were change in diagnosis for one patient and one patient who was ineligible after randomization, who did not receive any study treatment.[4]

Abbreviations: BV – brentuximab vedotin; C – cyclophosphamide; H – doxorubicin; n – number; O – vincristine; P – prednisone

Source: submission materials (clinical summary[5] and CSR[4])

b) Limitations/Sources of Bias

- Overall, the ECHELON-2 trial was well-conducted. The primary objective of the trial was to compare the PFS as determined by IRF between the two treatment groups, which was appropriately carried out. The randomization and allocation concealment methods were appropriately performed as were all levels of blinding, including administration of placebo drugs through the use of a pharmacy mask at each study site. At baseline, patients in both the BV+CHP and CHOP groups had similar demographics, disease-specific, and patient characteristics.
- The primary outcome of PFS per IRF 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. All measurements of efficacy employed standardized and internationally accepted criteria for the evaluation of lymphoma to assess tumour lesion size and extent of disease in the determination of progression and response rate.[58] Tumour imaging

was also consistent with general oncology practice, and an independent third-party core laboratory performing blinded review was used to ensure unbiased application of the Cheson 2007 response criteria.[4] The primary efficacy analysis was appropriately performed on the ITT population; patients included were analyzed according to treatment assignment at randomization, regardless of the actual treatment received. The safety analysis set also appropriately included all patients who received any amount of BV or any component of CHOP. These patients were analyzed according to the actual treatment received, regardless of which group they were randomized to.

- A detailed statistical analysis plan was described in the published report of the trial and an Independent Data Monitoring Committee monitored safety and assessed the results of an interim analysis for futility, which was performed when approximately 50% of patients had completed EOT.[2] The interim futility analysis occurred on May 31, 2015 and was based on efficacy data for 201 patients and safety data for 293 patients.[3] The IDMC recommended that the study proceed without modifications based on the futility analysis.[3]
- 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+ sALCL with IPI score ≥2, ALK- sALCL, PTCL NOS, AITL, ATLL, EATL, and hepatosplenic TCL; however, this reimbursement request is for patients with: ALK+ sALCL with IPI score ≥2, ALK- sALCL, PTCL NOS, and AITL only. Therefore, the request is for a large subpopulation (ALK+ sALCL with IPI score ≥2, ALK- 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 sub-type. Although the primary and key secondary outcome (OS) were also reported by PTCL sub-type, there is significant uncertainty in these results as the study was not designed to test specific hypotheses for these subgroups.[3] Combining all subgroups into one group, regardless of PTCL sub-type, discounts the potential for clinical heterogeneity in disease processes or the potential for differences in prognostic heterogeneity depending upon the specific PTCL sub-type.[7] The subgroup analysis of sALCL for PFS was the only subgroup for which an alpha controlled hypothesis test was pre-specified.[3]
- A total of 65 patients (29%) in the BV+CHP group and 96 patients (42%) in the CHOP group received subsequent anticancer therapy.[2] Of those patients that received subsequent therapy, 59 patients (26%) in the BV+CHP group and 94 patients (42%) in the CHOP group received systemic therapy for residual or progressive disease and among those patients, 23 (10%) in the BV+CHP group and 49 (22%) in the CHOP group received BV-containing regimens. Receipt of subsequent therapies could potentially confound the OS analysis as it is unknown if survival was prolonged due to BV+CHP or CHOP therapies or the subsequent anticancer therapies, or the sequential use of the therapies. The sponsor noted that despite the higher proportion

of patients who received subsequent BV in the CHOP group, the ECHELON-2 study demonstrated superior OS of BV+CHP versus CHOP.[3]

- 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.

- The statistical analysis plan describes the handling of dropouts and missing data, which were not imputed with the exception of AE dates and new anticancer therapy start dates for analysis of PFS. Imputation of new anticancer therapy start dates did not impact analysis of PFS, as no PFS events were based on an imputed start date for new anticancer therapy.[54] HRQoL outcomes were exploratory endpoints. The ECHELON-2 trial was not designed to test specific hypotheses for HRQoL outcomes and no firm conclusions can be drawn from these results.

- While significant effort was made to reduce the probability of bias in the trial, the possibility of sponsorship bias can not be overlooked. As is often the case with clinical trials funded by pharmaceutical companies, the majority of contributors to the study design, maintenance of study quality, data analysis, and the study report received personal or professional funds from the study sponsor.[2] Such conflicts of interest do raise some concerns.[8] Overall, numerous precautions were taken to minimize the risk of many forms of bias commonly encountered in randomized controlled trials. The procedures used in the ECHELON-2 study, including appropriate methods for randomization, blinding, overall study methodology, and statistical power of the study suggest that one can be reasonably confident that the overall effect of significant improvement in PFS is due to the study intervention, brentuximab vedotin.

6.3.4 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

The efficacy outcomes in the ECHELON-2 trial are summarized in Table 6.8. As of the August 15, 2018 cut-off date, the median duration of follow-up was 36.2 months (95% CI, 35.9-41.8) at the primary efficacy analysis. [2]

PFS per independent review facility (IRF)

At the time of the data cut-off date, 219 patients (48%) had experienced a PFS event; 95/226 (42%) in the BV+CHP group and 124/226 (55%) in the CHOP group.[2] The PFS HR was 0.71 ([95% CI 0.54-0.93]; p=0.0110) (Figure 6.2). The Kaplan-Meier plot of PFS per IRF assessment shows BV+CHP having a greater than 2-year improvement in median PFS duration over CHOP. The median PFS per IRF was 48.20 months (95% CI: 35.15, -) in the BV+CHP group versus 20.80 months (95% CI: 12.68, 47.57) in the CHOP group.

Sensitivity analysis of PFS

A sensitivity analysis was reported in which patients who received subsequent SCT or consolidative radiotherapy were censored.[54] The median PFS per IRF in this sensitivity analysis was 36.24 months (95% CI: 18.04, –) in the BV+CHP group versus

13.57 months (95% CI: 9.13, 27.14) in the CHOP group.[54] The PFS HR was 0.71 ((95% CI 0.53-0.94); p=0.0167), which suggested that the PFS benefit remained for BV+CHP even when receipt of subsequent SCT or consolidative radiotherapy was treated as a censoring event.[54]

The estimated PFS rates were also reported at 6, 12, 24, and 36 months[2]. The rates (and 95% CI) comparing the BV+CHP group to the CHOP group, respectively, at the four time points are as follows: 6 months 82.1% (76.4, 86.6) versus 70.8% (64.3, 76.3); 12 months 71.7% (65.1, 77.2) versus 58.2% (51.4, 64.3); 24 months 61.4% (54.4, 67.6) versus 47.4% (40.6, 53.8); and 36 months 57.1% (49.9, 63.7) versus 44.4 (37.6, 50.9).[2]

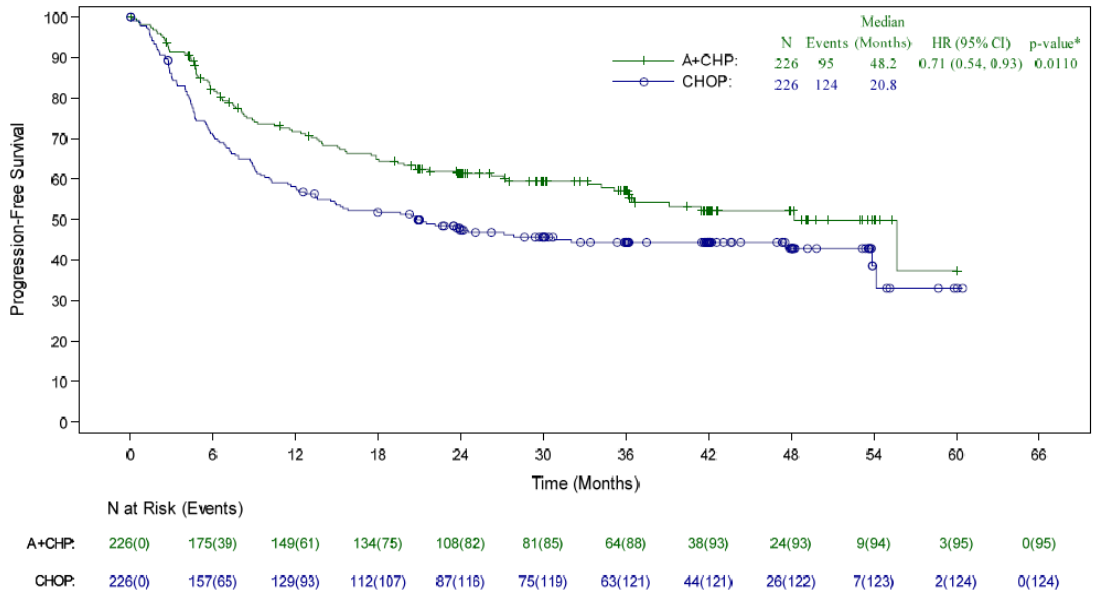
PFS per IRF in pts with sALCL

The results of the pre-specified and type 1 error controlled analysis of PFS per IRF for the sALCL subgroup of patients consistent with the results of the primary outcome of PFS[2]. The risk of PFS events in the sALCL subset was reduced by 41% in the BV+CHP group compared with the CHOP group (HR 0.59, 95% CI 0.42-0.84; p=0.0031)[4]. The Kaplan-Meier plot of PFS per IRF for subjects with sALCL is presented in Figure 6.3. The median PFS per IRF for subjects with sALCL was 55.66 months (95% CI: 48.20, –) on the BV+CHP group versus 54.18 months (95% CI: 13.44, –) on the CHOP group.[4] In both groups, the median PFS was driven by one event, with only 5 subjects at risk of an event in each group and is therefore not a representative outcome.[4] The 75th percentile of PFS was 15.6 months with BV+CHP compared to 4.6 months with CHOP.[4] Progression-free survival per IRF for subjects with sALCL was significantly improved in the A+CHP group compared with the CHOP group (stratified HR 0.59 [95% CI: 0.42, 0.84], P=0.0031).[4].

PFS per IRF in key prespecified subgroups

The prespecified groups for which PFS was calculated included IPI score (0-1, 2-3, 4-5), age (<65 years and ≥65 years), baseline ECOG status (0-1, 2), sex (male/female), disease stage (1-2, 3, 4), and disease indication (Alk-positive sALCL, Alk-negative sALCL, AITL, PTCL-NOS)[2]. Most results of the PFS subgroup analyses were consistent with the results of PFS in the ITT population except for the IPI score 4-5 and disease indication AITL subgroup results with PFS HRs > 1. However, it is important to note that 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.

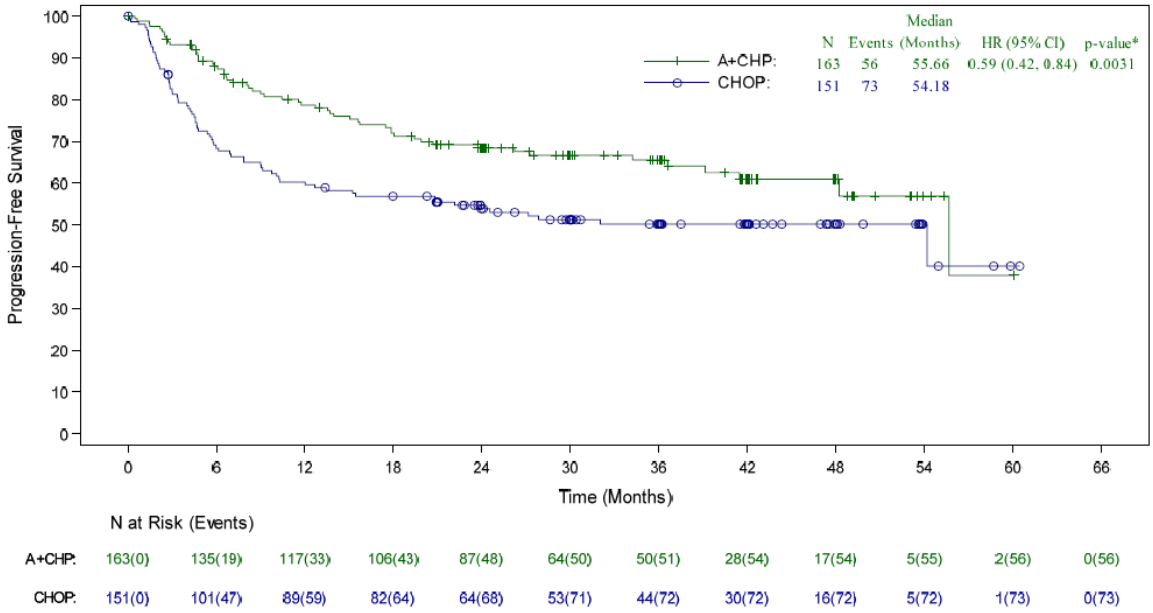
Figure 6.2: Kaplan-Meier Curve of IRF-Assessed Progression-Free Survival



* Computed from log-rank test using stratification factors (ALK-positive sALCL: Yes/No and IPI score: 0-1/2-3/4-5) at randomization

Source: FDA[59]

Figure 6.3: PFS per IRF for subjects with sALCL (ITT analysis set)



* Computed from log-rank test using stratification factors (ALK-positive sALCL: Yes/No and IPI score: 0–1/2–3/4–5) at randomization

Source: Submission materials (CSR)[4]

Table 6.8. Efficacy outcomes in the ECHELON-2 trial.[59]

Outcomes per IRF	BV+CHP N=226	CHOP N=226
Data cut-off date	August 15, 2018	
PFS		
Number of events, n (%)	95 (42)	124 (55)
Median PFS, months (95% CI)	48.2 (35.2, NE)	20.8 (12.7, 47.6)
Hazard ratio (95% CI)	0.71 (0.54, 0.93)	
p-value	0.011	
Reason leading to a PFS event, n (%)		
Progressive disease	71 (31)	86 (38)
Death	13 (6)	17 (8)
Receipt of subsequent anticancer chemotherapy to treat residual or PD	11 (5)	21 (9)
PFS for patients with sALCL		
N	163	151
N of patients with a PFS event, n (%)	56 (34)	73 (48)
Median PFS, months (95% CI)	55.7 (48.2, NE)	54.2 (13.4, NE)
Hazard ratio (95% CI)	0.59 (0.42, 0.84)	
p-value	0.003	
OS		
Number of deaths	51 (23)	73 (32)
Median OS, months (95% CI)	NE (NE, NE)	NE (54.2, NE)
Hazard ratio (95% CI)	0.66 (0.46, 0.95)	
p-value	0.024	
CR rate		
N[6] (%, 95% CI)	153 (68%, 61-74)	126 (56%, 49-62)
p-value	0.007	
ORR		
N[6] (%, 95% CI)	188 (83%, 78-88)	163 (72%, 66-78)
p-value	0.003	

Notes:

Abbreviations: CI – confidence interval; CR – complete remission; IRF – independent review facility; N – number; NE – not estimable; ORR – objective response rate; OS – overall survival; PD – progressive disease; PFS – progression-free survival;

P-value > 0.05 considered statistically significant.

Source: FDA[59] and clinicaltrials.gov[6]

Overall Survival

Overall survival, which was a key secondary outcome, was defined as the time from randomization to death due to any cause.[55] Any patient for whom death was not already known was censored for OS on the date the patient was last known to be alive, or the data cut-off date. Patients for whom there were data lacking beyond the day of randomization were censored on the date of randomization (i.e., OS duration of 1 day).[55] A significant survival advantage was demonstrated with treatment with BV+CHP compared to treatment with CHOP (HR 0.66, 95% CI 0.46-0.95; p=0.0244) (Figure 6.4). Since the data cut-off date, 51 (23%) deaths occurred in the BV+CHP group and 73 (32%) occurred in the CHOP group for a total of 124 (27%) deaths.[2] With a follow-up of 42.1 months (range 40.4-43.8), the median OS was not reached in either treatment group.[2] The estimated survival rate at 6 months was 93.7% (95% CI 89.6-96.2) in the BV+CHP group and 89.2% (95% CI 84.4-92.7) in the CHOP group. At 12 months, the estimated overall survival rate in the BV+CHP group was 87.8% (95% CI 82.8-91.5) and 82.4% (95% CI 76.7-86.8) in the CHOP group. At 24 months, the estimated overall survival rates were 80.8% (95% CI 75.0-85.5) and 72.6% (95% CI 66.2-78.0) in the BV+CHP and CHOP groups, respectively. At 36 months, the estimated OS was 76.8% (95% CI 70.4-82.0) compared to 69.1% (95% CI 62.3-74.9) in the BV+CHP and CHOP groups, respectively.[2]

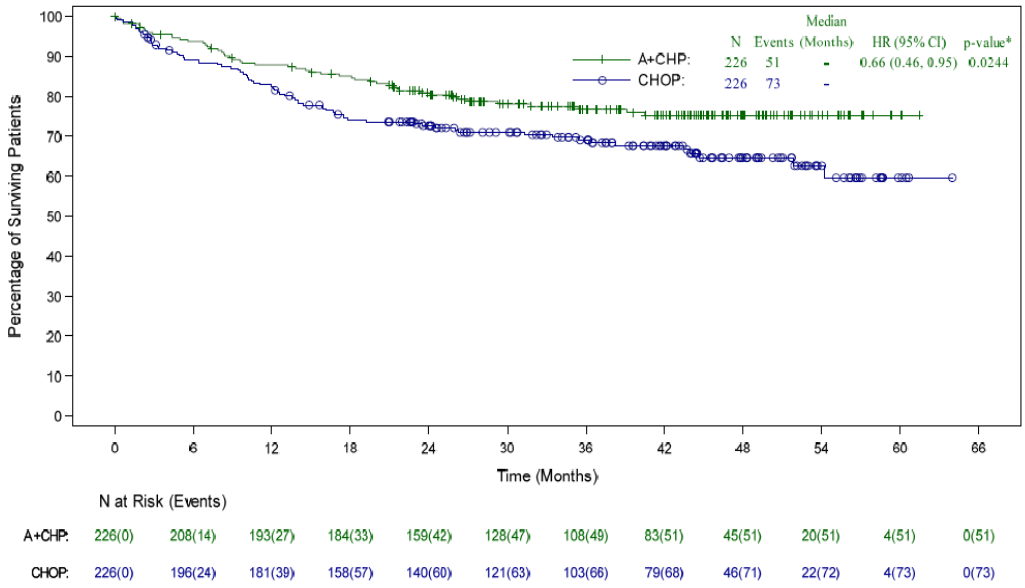
OS in key prespecified subgroups

The prespecified groups for which OS was calculated included IPI score (0-1, 2-3, 4-5), age (<65 years and ≥65 years), baseline ECOG status (0-1, 2), sex (male/female), disease stage (1-2, 3, 4), and disease indication (Alk-positive sALCL, Alk-negative sALCL, AITL, PTCL-NOS)[2]. Most results of the OS subgroup analyses were consistent with the results of OS in the ITT population except for the IPI score 4-5 and ECOG 2 subgroup results with OS HRs > 1. However, it is important to note that subgroup analyses for OS are considered exploratory because the ECHELON-2 trial was not designed to test specific hypotheses for subgroups in OS. The purpose of the exploratory subgroup analyses is hypothesis generating only.

Sensitivity analysis of OS

A total of 27% of patients in the BV+CHP group and 19% in the CHOP group received post-treatment consolidative treatments. Among these patients, consolidative SCT was received by 22% and 17% and consolidative radiotherapy was received by 6% and 3% of subjects in the BV+CHP and CHOP groups, respectively.[2] To examine any confounding effect from consolidative treatments on OS results, a sensitivity analysis was conducted that censored patients at the time of receipt of consolidative treatment (consolidative radiotherapy, consolidative SCT) as determined by the blinded investigator.[56] The results of this analysis were consistent with the primary OS analysis.[56] This suggested that the OS benefit observed with BV+CHP appears to be robust even when patients were censored at the time of receipt of consolidative treatment.

Figure 6.4: Overall Survival



* Computed from log-rank test using stratification factors (ALK-positive sALCL: Yes/No and IPI score: 0–1/2–3/4–5) at randomization.

Source: FDA[59]

Complete remission (CR) rate and objective response rate (ORR) per IRF at end of treatment

The CR rate was defined as the proportion of subjects with CR per IRF following the completion of study treatment (at end of treatment or at the first assessment after the last dose of study treatment and prior to long-term follow-up) according to the Revised Response Criteria for Malignant Lymphoma[58].[55] Radiographic disease evaluations, including computed tomography (CT) scans of the neck, chest, abdomen and pelvis, were assessed at the following timepoints: baseline, after the 4th cycle of treatment, at completion of treatment, at 9, 12, 15, 18, 21, and 24 months after initiation of treatment, and every 6 months thereafter until disease progression, death, or analysis of the primary endpoint, whichever occurred first. A CT scan was also performed at the time of suspected clinical progression. A PET scan was required at baseline, after cycle 4, and at completion of treatment.[55]

The CR and ORR favoured treatment with BV+CHP versus CHOP and the differences were statistically significant (Table 6.8).[2] A significantly greater CR was detected in the treatment group compared to the control group (68% versus 56%, p=0.007, respectively). Furthermore, the ORR at the end of treatment in the brentuximab group was significantly higher at 83% compared to 72% in the CHOP group (p=0.003).[2]

Quality of Life

In the ECHELON-2 trial, HRQoL was an exploratory endpoint and was measured using the following instruments: EORTC Quality of Life Questionnaire-Core 30 (QLQ-

C30), the FACT/GOG-NTX, and the European Quality of Life 5-Dimensions Questionnaire (EQ-5D-3L).[5]

The EORTC QLQ-C30 instrument consists of five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), a global health status / QoL scale, as well as questions assessing additional symptoms commonly reported by cancer patients (dyspnoea, loss of appetite, insomnia, constipation and diarrhoea) and financial impact of cancer.[60] Higher scores reflect improvement.[5] The EORTC-QLQ-C30 was administered at baseline, at day 1 of every treatment cycle[4], every 3 months (+/- 1 week) month 9 through month 24 and at month 30, or until disease progression.[55] The sponsor applied a minimally important difference (MID) for a mean change in score of 10, referencing a published study from by Osoba et al. (1998)[61]. [5]

The EQ-5D consists of a visual assessment scale to assess overall health status, and the 5-dimensional score, which assesses health status in terms of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.[55] High scores signify a high level of functioning and better health states.[5] The EQ-5D was administered at baseline, at day 1 of every treatment cycle, every 3 months (+/- 1 week) month 9 through month 24 and every 6 months (+/- 1 week) thereafter.[55] The questionnaire was not required to be administered at months 9, 15, and 21 for patients with disease progression.[55] The sponsor applied a published minimally important difference (MID) from a study by Pickard et al. (2007) which reports the MID as 0.08 for UK-based scores, 0.06 for US-based scores, and 0.07 for VAS scores.[5,62]

The FACT/GOG-NTX instrument assessed changes in quality of life plus an eleven-item subscale (Ntx subscale) that assessing the symptoms and concerns associated specifically with chemotherapy-induced neuropathy.[63] High scores on the EORTC-QLQ-C30 functional scales, which include emotional, role, physical, social and cognitive, and the global health status correspond to both a high level of functioning and high quality of life while high scores on the symptom scales represent a higher impact of symptoms on quality of life.[5] The FACT/GOG-NTX was administered at baseline, at day 1 of every treatment cycle[4], every 3 months(+/_ 1 week) months 9 through month 24 or until disease progression or initiation of new anticancer therapy. This questionnaire was only administered to patients with treatment-emergent neuropathy.[55]

The descriptive HRQoL analyses were conducted in the ITT population.[4] Statistical modeling was performed as post hoc analyses.[57] The overall response rate for the patient-reported outcomes questionnaires was high (>90%) in both treatment groups[5] 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 months 24.[4]

The mean EORTC symptom, functional, and global health scores were lower at baseline in the BV+CHP group compared with the CHOP group.[5] 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 MID of 10.[61] The differences in favour of CHOP were in global health status (during Cycle 6), role functioning (during

Cycles 2 through 6), social functioning (during Cycles 2, 3, and 6), total score (during Cycle 2), appetite loss (during Cycle 5), nausea and vomiting (during Cycles 2 and 7), diarrhea (during Cycles 2 and 7), and pain (during Cycles 2, 3, and 4). No statistically significant differences were detected in other functional or symptom scales. Over time, within both the BV+CHP and CHOP groups, there was a trend towards lower total or subscale scores for patients who had a progression event, compared with those who did not but overall the differences did not reach the MID.[5]

For the FACT/GOG-NTX neurotoxicity subscale, the sponsor noted that scores were not meaningfully different between the treatment groups up to Cycle 8.[5] At the end of treatment visit, the score was lower for the brentuximab group compared with the CHOP group, which is in line with the higher rate of unresolved neuropathy in the BV+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. In relation to PFS events, no difference in FACT/GOG-NTX subscale scores was detected over time in both treatment groups for subjects who experienced a PFS event versus those who did not.[5]

Data from both the EQ-5D and the EQ-VAS were included in the EQ-5D-3L. Furthermore, the EQ-5D time trade-off (TTO) indexed data were analyzed using both US- and UK-based value sets.[5] In comparison with the CHOP group, the mean baseline score was lower for the BV+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. No difference was observed in either treatment group in EQ-5D TTO-indexed data, analyzed using US- or UK-based value sets for patients who did, versus those who did not experience a PFS event.[5]

Harms Outcomes

Toxicity

Safety was assessed through the recording and surveillance of adverse events (AEs) and measurement of physical examination findings and laboratory tests.[55] The incidence of AEs was summarized by system organ class, preferred term, severity, seriousness, and relationship to the study drug.[55] An overall summary of AEs from the safety analysis set (which included 223 subjects who received any amount of BV and 226 subjects who received any component of CHOP) is presented in Table 6.9.

The most common treatment-emergent adverse events (TEAE) occurring in ≥10% of patients in the BV+CHP group are presented in Table 6.9.[4] Almost all patients in both treatment groups experienced a TEAE (99% and 98% of patients in the BV+CHP and CHOP groups, respectively). The most frequently occurring TEAEs in the BV+CHP and CHOP groups, respectively, included nausea (n=103 [46%] versus n=87 [38%]), peripheral sensory neuropathy (n=100 [45%] versus n=92 [41%]), diarrhea (n=85 [38%] versus n=46 [20%]), neutropenia (n=85 [38%] versus n=85 [38%]), and constipation (n=64 [29%] versus n=67[30%]).[4]

There was a comparable number of adverse events ≥ Grade 3 reported between both trial groups.[4] A total of 147 (66%) patients in the BV+CHP group and 146 (65%)

patients in the CHOP group experienced at least one adverse event ≥ Grade 3 (occurring in ≥2% of subjects in the BV+CHP group as part of the safety analysis set)[4]. Neutropenia, febrile neutropenia, and anemia were among the most common ≥ Grade 3 adverse events (Table 6.9). Of the 147 patients in the BC+CHP group who had Grade 3 or higher AEs, 62 (42%) had Grade 4 events and 8 (5%) had Grade 5 (fatal) events. This is compared to 63 (43%) patients in the CHOP group experiencing Grade 4 events and 16 (11%) Grade 5 (fatal) events.[4]

The number of serious adverse events (SAE) was comparable between treatment groups (Table 6.9).[4] The most frequently reported SAEs that occurred in ≥2 patients in the BV+CHP group were febrile neutropenia (14%), pneumonia (5%), pyrexia (4%), and neutropenia (4%). The corresponding proportion of patients in the CHOP group experiencing the same SAEs was 12% (febrile neutropenia), 1% (pneumonia), 3% (pyrexia), and 3% (neutropenia).[4]

Comparable discontinuation rates were reported between both groups of the trial, with a total of 29 patients (6%) having experienced an adverse event that resulted in treatment discontinuation; 14 patients (6%) in the BV+CHP group and 15 patients (7%) in the CHOP group.[2] Adverse events leading to dose reductions, delays, or interruptions were similar between trial groups, and are summarized in Table 6.9. The most common reason for dose delays of blinded study drug in the BV group was occurrence of an adverse event, which was reported for 59 (26%) patients; specific adverse events most commonly reported as leading to dose delays were neutropenia (5%), pneumonia (3%), and pyrexia (2%). In the CHOP group, 28 (12%) patients experienced dose delays and the main reasons were neutropenia (4%), leukopenia (2%), and pyrexia (2%).[4]

As of the August 15, 2019 data cut-off date, a total of 123 deaths had been reported in patients treated on either group, 50 in the BV+CHP group and 73 in the CHOP group[4]. One additional patient in the BV+CHP group died after randomization but before receiving the study treatment. This patient is included in the OS analysis. In the BV+CHP group, 36 deaths were disease related, 10 were not disease related, and the disease relationship was unknown for 4 patients. In the CHOP group, 58 deaths were disease related, 7 were not disease related, and the disease relationship was unknown for 8 patients.[4]

The number of patients with pre-existing peripheral neuropathy was similar between groups (BV+CHP, n=24 (11%) versus CHOP, n=25 (11%)[2]. Treatment-emergent peripheral neuropathy (TEPN) was slightly less frequent in the BV+CHP group at 117 (52%) patients compared with 124 (55%) patients in the CHOP group.[2] The majority of TEPN events were Grade 1.Treatment-related peripheral neuropathy was also similar between groups (BV+CHP, n=112 (50%) versus CHOP, n=111 (49%)).[4] Both treatment groups had the same number (n=16) and proportion (7%) of patients experiencing dose modifications due to peripheral neuropathy.[2]

For the prophylactic management of patients developing neutropenia, the use of G-CSF was allowed per protocol according to institutional guidelines.[2] G-CSF was administered for primary prophylaxis to 75 (34%) of patients in the BV+CHP group and 61 (27%) of patients in the CHOP group.[5] Febrile neutropenia was reported for 16% of patients in the BV+CHP group who received primary prophylaxis with G-CSF compared with 20% of BV+CHP patients who did not receive prophylactic treatment[2]. The results were similar for the CHOP group (11% versus 16%). A total of 13% of patients in the BV+CHP group who received G-CSP prophylaxis reported ≥Grade 3 neutropenia versus 45% of patients who did not receive prophylaxis. Again, the results were similar for the CHOP group (13% versus 42%).[2]

Table 6.9 Toxicity outcomes in the ECHELON-2 trial.

	ECHELON-2	
	BV+CHP (n=223)	CHOP (n=226)
Duration of treatment[a] (w), median	18.1	18.0
No. of treatment cycles per pt, median	6.0	6.0
AE, n (%)		
Any TEAE[b] (reported for ≥10% pts in BV+CHP group)	221 (99)	221 (98)
Nausea	103 (46)	87 (38)
Peripheral sensory neuropathy	100 (45)	92 (41)
Diarrhea	85 (38)	46 (20)
Neutropenia	85 (38)	85 (38)
Constipation	64 (29)	67 (30)
Alopecia	58 (26)	56 (25)
Pyrexia	58 (26)	42 (19)
Vomiting	57 (26)	39 (17)
Fatigue	54 (24)	46 (20)
Anemia	46 (21)	36 (16)
Febrile neutropenia	41 (18)	33 (15)
Dyspnea	32 (14)	24 (11)
Any BV or vincristine-related event[c] (≥10% pts)(TRAE)	201 (90)	193 (85)
Peripheral sensory neuropathy	98 (44)	87 (38)
Neutropenia	75 (34)	68 (30)
Nausea	71 (32)	61 (27)
Constipation	47 (21)	50 (22)
Alopecia	38 (17)	30 (13)
Diarrhea	36 (16)	16 (7)
Grade ≥3 TEAEs (occurring in ≥2% pts in BV+CHP group)	147 (66)	146 (65)
Neutropenia	77 (35)	76 (34)
Febrile neutropenia	41 (18)	33 (15)
Anemia	30 (13)	23 (10)
Diarrhea	13 (6)	2 (1)
Pneumonia	12 (5)	5 (2)
Peripheral sensory neuropathy	8 (4)	6 (3)
Any serious AEs (occurring in ≥2% pts in BV+CHP group)	87 (39)	87 (38)
Febrile neutropenia	31 (14)	26 (12)
Pneumonia	11 (5)	3 (1)
Pyrexia	9 (4)	7 (3)
Neutropenia	8 (4)	6 (3)
Any grade ≥3 BV or vincristine-related event[c]	116 (52)	104 (46)
Patients with AEs resulting in BV or vincristine dose modification, n (%)		
Dose reduced	21 (9)	24 (11)
Dose delayed	59 (26)	28 (12)
Dose discontinued	4 (2)	5 (2)
Treatment discontinuation due to AEs	14 (6)	15 (7)
Death due to AEs	8 (4)	16 (7)

Notes:
[b] – treatment-emergent AEs defined as newly occurring (not present at baseline) or worsening after the first dose of BV or any component of multiagent chemotherapy (CHP or CHOP)
[c] – related to treatment as assessed by the investigator
Abbreviations: AE – adverse event; BV – brentuximab vedotin; n - number; pt – patient; SD – standard deviation; TEAE – treatment-emergent adverse event; TRAE – treatment-related adverse event; w – weeks

Source: pCODR submission (CSR)[4] and Horwitz et al. (2018)[2]

6.4 Ongoing Trials

No ongoing trials were identified.

7 SUPPLEMENTAL QUESTIONS

The pCODR CGP and the pCODR Methods Team did not identify supplemental questions.

8 COMPARISON WITH OTHER LITERATURE

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

pCODR 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 pCODR Disclosure of Information Guidelines. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report.

The Lymphoma Clinical Guidance Panel is comprised of three clinical oncologists. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the CADTH website (www.cadth.ca/pcodr). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY AND DETAILED METHODOLOGY

1. Literature search via Ovid platform

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** September 2019**, Embase** 1974 to 2019 October 17**, Ovid MEDLINE(R) ALL** 1946 to October 17, 2019

#	Searches	Results
1	(Brentuximab* or Adcetris* or adtsetrys* or SGN-35 or SGN35 or cAC10-vcMMAE or CAC10-1006 or 7XL5ISS668).ti,ab,ot,kf,kw,hw,rn,nm.	4712
2	Lymphoma, T-Cell, Peripheral/	3597
3	((t-cell* or tcell*) adj4 (leukem* or leukaem* or lymphom* or neoplas* or malignan*) adj6 peripheral).ti,ab,kf,kw.	9483
4	PTCL.ti,ab,kf,kw.	5137
5	or/2-4	12039
6	1 and 5	326
7	6 use medall	60
8	limit 7 to english language	58
9	6 use cctr	19
10	8 or 9	77
11	*Brentuximab vedotin/ or (brentuximab* or adcetris* or adtsetrys* or SGN-35 or SGN35 or cAC10-vcMMAE or CAC10-1006).ti,ab,kw,dq.	3335
12	peripheral T cell lymphoma/	5782
13	((t-cell* or tcell*) adj4 (leukem* or leukaem* or lymphom* or neoplas* or malignan*) adj6 peripheral).ti,ab,kw,dq.	9461

14	PTCL.ti,ab,kw,dq.	5126
15	or/12-14	12582
16	11 and 15	246
17	16 use oemezd	173
18	limit 17 to english language	163
19	18 not (conference review or conference abstract).pt.	90
20	10 or 19	167
21	remove duplicates from 20	113
22	18 and (conference review or conference abstract).pt.	73
23	limit 22 to yr="2014 -Current"	56
24	21 or 23	169

2. Literature search via PubMed

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

Search	Query	Items Found
#5	Search #3 AND #4	0
#4	Search Publisher[sb]	400234
#3	Search #1 AND #2	36
#2	Search Lymphoma, T-Cell, Peripheral[MeSH] OR peripheral t-cell lymphoma*[tiab] OR peripheral tcell lymphoma*[tiab] OR peripheral t-cell leukemia*[tiab] OR peripheral tcell leukemia*[tiab] OR peripheral t-cell leukaemia*[tiab] OR peripheral tcell leukaemia*[tiab] peripheral t-cell neoplas*[tiab] OR peripheral tcell neoplas*[tiab] OR peripheral t-cell malignan*[tiab] OR peripheral tcellmalignan*[tiab] OR PTCL[tiab]	2209
#1	Search brentuximab vedotin [Supplementary Concept] OR brentuximab[tiab] OR Adcetris*[tiab] OR adtsetrys*[tiab] OR SGN-35[tiab] OR SGN35[tiab] OR cAC10-vcMMAE[tiab] OR 7XL5ISS668[rn]	930

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/

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
http://www.canadiancancertrials.ca/

Search: Adcetris/ brentuximab vedotin, peripheral T-cell 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, peripheral T-cell 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, peripheral T-cell 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).[64]

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 and peripheral T-cell lymphoma.

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

The search is considered up to date as of February 20, 2019.

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).[65] 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 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), American Society of Hematology (ASH) and the European Society for Medical Oncology (ESMO) 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 pCODR 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 independently made the final selection of studies to be included in the review and differences were resolved through discussion.

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 pCODR 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 the pCODR Secretariat:

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

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